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Search for genetic and environmental factors predictive of adult psychopathy in a clinical sample of callous-unemotional youths with conduct disorder as compared to populations of incarcerated adolescents and adults

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Abstract

Psychopathy has been conceptualized as a constellation of traits that can be differentiated into interpersonal (e.g., manipulative personality, pathological lying), affective (e.g., callousness/lack of empathy), lifestyle (e.g., irresponsibility, poor behavioral control), and antisocial (e.g., early behavioral problems) dimensions. Though psychopathy has been primarily studied in adult samples, one of the main goals of the current psychiatric research is to identify early signs in youths useful to predict psychopathy in adulthood. Many core features of psychopathy, indeed, as for example low empathy, are often related to behavioral problems and aggression in children. This field of research primarily focuses on children with conduct disorder (CD), who are known to be at risk of developing life-course-persistent antisocial problems, mostly if they show callous-unemotional (CU) traits that are cognitive, affective, social, and personality characteristics resembling the adult affective dimension of psychopathy.

My PhD work focused on the investigation of the genetic and environmental correlates of psychopathy from childhood to adulthood with the aim of identifying genetic biomarkers that could be early predictors of psychopathy. To this aim, 14 polymorphisms belonging to the serotonergic (*5-HTR1B* rs13212041, *5-HTR2A* rs6314, *MAOA* uVNTR, 5-HTTLPR, *TPH2* rs4570625), dopaminergic (*ANKK1* rs1800497, *COMT* rs4680, *DRD4* exonIII VNTR, *DRD4* rs1800955, *TH* rs6356, *SLC6A3* 40bp VNTR), and oxytonergic (*OXTR* rs53576, rs1042778, rs237885) pathways were genotyped in three groups of subjects, each of them representative of a different age of life: a) 985 White male incarcerated adults (19-65 years old) that are the largest sample of criminals studied so far; b) 180 White male incarcerated adolescents (14-18 years old); and c) 120 White male youths with CD (7-16 years old). Psychopathic traits were assessed in incarcerated adults by the Psychopathy Checklist-Revised (PCL-R) questionnaire, in incarcerated adolescentsby the Psychopathy Checklist:Youth Version (PCL:YV), and in CD youths by the Antisocial Process Screening Device (APSD). Youths were also assessed for CU traits by the APSD-CU subscale. Finally, in a subgroup of 247 incarcerated adults, the *Measure of Parental Style* (MOPS) questionnaire was used to measure the perceived behavior of their parents during the first 16 years of life, while, in CD youths, maltreatment data were collected by the Maltreatment Index (MI) scale.

The results of my thesis work showed that the *5-HTR1B* rs13212041 T/T genotype increased the risk of psychopathy in both incarcerated adults and incarcerated adolescents; in

incarcerated adults, childhood paternal maltreatment positively correlated with psychopathy scores and this correlation was stronger in interaction with the *5-HTR1B* rs13212041 T/T genotype, the *ANKK1* rs1800497 T allele, the *OXTR* rs53576 A allele, or the *TH* rs6356 G/G genotype; specific combinations of these risk alleles, such as *5-HTR1B* rs13212041 T/T by *ANKK1* rs1800497 T allele by *TH* rs6356 G/G and *5-HTR1B* rs13212041 T/T by *TH* rs6356 G/G by *OXTR* rs53576 A allele, synergistically increased the correlation between paternal maltreatment and high psychopathy scores.

Interestingly, in children exposed to active maltreatment, the *ANKK1* rs1800497 T allele, both per se and in interaction with the *5-HTR1B* rs13212041 T/T genotype, was associated with CU trait scores that exceeded the diagnostic cut-off of the APSD-CU subscale.

The scientific literature suggests that the identified risk alleles are associated with an increased dopamine and serotonin release. We hypothesized that a greater availability of these neurotransmitters modulated by genetics, make children more receptive to maltreatment, increasing further their risk of developing psychopathy.

In conclusion, my Ph.D. work indicates that interaction among the *5-HTR1B* rs13212041 T/T genotype, the *ANKK1* rs1800497 T allele, and childhood maltreatment is a significant correlate of psychopathic traits from childhood to adultness, thus proposing these two genetic variants as potential biomarkers of developmental life-lasting psychopathy. These findings might help improve the success rate of preventing youths with CD from developing psychopathy as adults throught more intense preventive behavioral treatments tailored to increase the child's empathic abilities and re-educate parental behavior.

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Chapter 1

Introduction

1.1 Characteristics of psychopathic traits

Psychopathy is a condition characterized by a constellation of atypical emotions and socially maladaptive behavioral patterns. Individuals with psychopathic traits show grandiose, superficial, and manipulative behavior, shallow affect, lack of empathy, remorse, and guilt, as well as impulsive, irresponsible, aggressive, and rule-breaking behavior with criminal inclination (Hare & Newman, 2009). The gold standard psychometric questionnaire for the assessment of psychopathy, namely the Psychopathy Checklist-Revised (PCL-R by Robert Hare, 2003), describes psychopathy as a bi-dimensional construct characterized by interpersonal/affective deficits (measured by the Factor 1 subscale of PCL-R) and lifestyle/antisocial tendencies (measured by the Factor 2 subscale of PCL-R).

Psychopathy is not listed as a diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, Fifth edition; APA, 2013). Psychopathy shares some characteristics with the Antisocial Personality Disorder (ASPD), which describes individuals showing disregard for and violation of the rights of others (Fazel & Danesh, 2002). The link between ASPD and psychopathy is actually controversial; most subjects with psychopathic traits, indeed, satisfy the diagnostic criteria of ASPD, but only a minority of those with an ASPD diagnosis are classified as individuals with psychopathic traits (Ogloff, 2006; Ogloff et al., 2016). ASPD highly overlaps with the impulsive/antisocial aspects, while the affective deficits, such as callousness and lack of empathy, are usually absent in ASPD patients (Ogloff, 2006). Therefore, affective deficits represent a core feature of psychopathy but not of ASPD.

Affective deficits are risk factors for antisocial and criminal behaviors, especially characterized by violence (van Zonneveld et al., 2017; Ortiz Baron et al., 2018; Gandhi et al., 2021; Cunha, Braga, & Gonçalves, 2021). In the US, for example, psychopathy has been observed in about 15-25% of the prison population (Theodorakis, 2013), while the percentage in the general population is about 4.5%, as observed across multiple countries (Sanz-Garcia et al., 2021). Moreover, psychopathy has been detected more frequently in males than females (Sanz-Garcia et al., 2021).

Incarcerated criminals with psychopathic traits are 15-25 times more likely to reoffend (Kiehl & Hoffmann, 2011). Indeed, if offenders usually tend to gradually decrease their criminal behavior as they get older, those with psychopathy do not show this age-related reduction in engaging in violent acts (Hare, 2001).

Furthermore, institutionalized subjects with psychopathic traits are more likely to be conditionally released (Kiehl & Hoffmann, 2011; Shepherd et al., 2018) because of their abilty to persuade parole boards to release them to the community through superficial sham, lies, and fake remorse or guilt (Porter at al., 2009). However, when released, offenders with psychopathic traits are not able to inhibit further criminal behaviors and, consequently, recidivate more often than offenders without psychopathy (Kiehl & Hoffmann, 2011; Shepherd et al., 2018). Their higher tendency to criminal recidivism has been hypothesized to be linked to a deficit in aversive conditioning (Blair et al., 2004). Aversive conditioning is a learning process that allows making associations between specific behaviors and consequent punishment, thus reducing further engagement in deleterious behaviors (Haxby et al., 2000; Vuilleumier & Pourtois, 2007). A reduced aversive inhibition has been associated with a deficient interaction between limbic-subcortical and cortical structures (Flor et al., 2002) and hypothesized to play a key role in the lack of inhibition toward the instrumental violent behavior that characterizes individuals with psychopathy (Birbaumer et al., 2005; Geurts et al., 2022).

The management of incarcerated subjects with psychopathy is particularly problematic as they are a "*challenging population to treat, who are often recalcitrant to change and at high risk for program non-completion*"-M.E. Oliver 2016 (Olver, 2016). High PCL-R Interpersonal/Affective scores have been associated with reluctance to engage in interventions (Tangney et al., 2011), and failure of treatments and educational training programs (Hare et al., 2000; Poythress et al., 2010; Olver et al., 2013; Olver et al., 2015). Psychopathy, indeed, characterizes individuals who do not feel they have psychological or emotional problems, are generally satisfied with themselves, and see themselves as superior beings in a world of inferiors (Maxmen et al., 2009). Moreover, offenders with psychopathic traits cannot be managed in ordinary prison settings, due to their persistent dangerous behavior that requires high security jails (Millon et al., 1998). For these reasons, psychopathy is identified by some authors as the most expensive mental condition and as a major public health problem (Kiehl, 2013); thus, its recognition and treatment should be a public health priority. Moreover, the misconception that offenders with psychopathy cannot be treated is not further supported by the most recent evidence (Berg et al., 2013). Neuroscientific research evidence, indeed, has suggested that psychopathy has a neurodevelopmental origin (Gao et al., 2009; Anderson & Kiehl, 2014), thus suggesting that therapeutic interventions may be much more

effective if administered at younger ages (Kiehl & Hoffmann, 2011). In the DSM-V (APA, 2013), psychopathic traits are described for several juvenile behavioral problems characterized by antisociality, like Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) (Frick et al. 2014_a; Willoughby et al. 2014). CD, in particular, is characterized by repetitive and persistent patterns of behaviors that violate the rights of others, including aggression, property damage, and rule-breaking behavior (Kazdin & Weisz, 2003). About 10-32% of children with CD show high levels of callous-unemotional (CU) traits (Kahn et al., 2012). CU traits are characterized by lack of empathy and guilt, failure to put the effort on important tasks, shallow affects, and deficient emotions; CU traits have been included in the fifth edition of the DSM-V, as a specifier for the diagnosis of CD, termed "Limited Prosocial Emotions" (Moore et al., 2019; Viding & McCrory, 2018). CU traits resemble the affective features of adult psychopathy (Hare & Newmann, 2008) and are relatively stable from childhood to adulthood, especially in children with severe CD (Blair, 2013; Frick et al., 2014_b; McMahon et al., 2010).

Contrarily to the common moral sense, CD youths with CU traits judge actions that cause harm to someone else morally acceptable (Thornberg & Jungert, 2017). Probably, they are not concerned about the suffering they can cause to other people and do not care about the perspective of being punished for their actions, even if they seem to be aware of this possibility (Thornberg & Jungert, 2017; Pardini & Byrd, 2012; Centifanti, 2012).

The co-occurrence of CD and CU traits has been associated with more severe and persistent antisocial behavior (Bamvita et al., 2021), especially "proactive aggression" (Lozier et al., 2014), which is a type of premeditated aggressive behavior frequently associated with psychopathy (Craig et al., 2021). The association between CU traits and proactive aggression seems to be mediated by the amygdala hypoactivation in response to emotional stimuli (Lozier et al., 2014). Reduced amygdala reactivity to emotional stimuli has been observed also in adults with psychopathy (Birbaumer et al., 2005; Contreras-Rodriguez et al., 2014). In addition, reduced connectivity between the amygdala and the prefrontal cortex characterizes both CU traits (Marsh et al., 2008) and psychopathy (Birbaumer et al., 2005; Volman et al., 2016).

CD youths with CU traits respond poorly to therapies (Hawes, Price, & Dadds, 2014). However, intensive and tailored interventions appear to reduce the severity of behavioral problems improving their empathic abilities (Dadds et al., 2012; Kimonis et al., 2019) and reducing their conduct problems and emotional deficits (White et al., 2013). Moreover, the education of parents to positive reinforcement and to warm parenting have been shown to be effective in promoting prosocial behavior (Hawes & Dadds, 2005) and emotional skills in these children (Hawes & Dadds, 2005; McDonald et al., 2011; Kimonis et al., 2019).

Overall, the scientific literature suggests that children with CD have a higher risk of developing life-course-persistent antisocial problems, mostly if they show CU traits. Moreover, the co-occurrence of CD and CU traits appears to be an early sign of persistent psychopathic traits throughout the life-course (Moore et al., 2019) predictive of adult psychopathy (Burke et al., 2007; Hawes et al., 2017). Deepening knowledge on the neurobiological roots of these behavioral problems could help guiding innovative treatments, thus improving the rate of success in preventing youths with CD to develop psychopathy as adults.

1.2 Heritability of psychopathic traits

The heritability of psychopathic traits has been estimated by several quantitative genetic studies conducted in twins and adoptees (for a recent comprehensive review see Moore et al., 2019). Twin studies compare identical and fraternal twins raised in the same family, assuming that monozygotic twins share 100% of their genome, while dizygotic twins share 50% of it; they allow for the estimation of additive (the sum of independent alleles) and non-additive (gene by gene interactions) genetic influences, as well as shared and non-shared environmental influences. Shared environments refer to mutual environments that make twins more similar to each other than randomly selected pairs of people, while non-shared environments are unique to each twin and are responsible for dissimilarities between them (Neale & Cardon, 1992).

A recent systematic review has shown that the etiology of CU traits is influenced by genetics, which explains from 36 to 68% of the CU trait variance. The remaining variance has been attributed to non-shared environmental factors (Moore et al., 2019). This wide range of variance linked to genetics can be explained by considering that, in different studies CU traits were measured by different questionnaires and samples differed for gender and age. Moreover, primary CU traits, characterized by lower anxiety and a history of neglect, and believed to be mostly influenced by genetics, were not always separated from secondary CU traits, characterized by higher anxiety, and influenced mostly by aversive experiences, such as severe physical and sexual abuse (Kimonis et al., 2013; Cecil et al., 2018).

As far as psychopathy is concerned, genetics has been shown to explain from 33 to 69% of the variance of psychopathy scores, while the rest has been attributed to non-shared environmental factors (Beaver et al., 2011; Larsson et al., 2007; Forsman et al., 2008; Hunt et al., 2015; Friedman et al., 2021).

Overall, the scientific literature shows that both CU traits and psychopathy are influenced by genetics and suggests that the genetic influence can be even greater for CU traits than psychopathy (Dhanani et al., 2018).

The stability of CU traits from childhood to adolescence and of psychopathy from early adolescence to late adolescence/early adulthood has been primarily attributed to genetics (Forsman et al., 2008; Henry et al., 2018; Takahashi et al., 2021). However, the heritability of CU traits has been shown to decrease with age (Henry et al., 2018; Takahashi et al., 2021).

The stability of behavior over time can be explained by two non-mutually exclusive models: (i) the *genetic set-point* model, where a single set of genetic factors are associated with behavior over time;

and (ii) the *genetic maturation* model, where novel genetic factors may emerge over time (Lacourse et al., 2014). According to these models, some genetic factors may significantly influence psychopathic traits already in childhood, while others may show up later in life (Henry et al., 2018; Takahashi et al., 2021). Thus, 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*"-Palumbo et al., 2022_a. Moreover, novel gene-by-gene and gene-by-environment interactions occur with aging (Takahashi et al., 2021), which, in turn, may modify previous effects of other genes, mitigating their influence (Hyde et al., 2016; Waller et al., 2016). This phenomenon, known as "genetic innovation", is thought to be a consequence of the brain maturation processes and hormonal, neuroanatomical, and neurochemical changes occurring during puberty (Takahashi et al., 2021; Spear, 2000).

1.2.1 Environmental risk factors of psychopathic traits

Experiencing traumas during childhood has been shown to have negative consequences on behavior; in particular, poor attachment, dysfunctional parenting, and severe maltreatment represent the most significant risk factors for the development of psychopathic traits as discussed below.

Attachment is a physiological process characterized by innate behaviors, such as crying and smiling, that promotes proximity of the child to its caregiver, essential for children to safely explore the environment and cope with life experiences (van der Zouwen et al., 2018). Secure attachment is created by warm and caring parents, whereas children with insensitive, inconsistently sensitive, and unpredictable caregivers show unsecure attachment (van der Zouwen et al., 2018). For example, low parental bonding were associated with adult psychopathy (Gao et al., 2010; Durand & de Calheiros Velozo, 2018) and high PCL-R Interpersonal/Affective scores were predicted by insecure attachment in criminal adults and adolescents (Frodi et al., 2001; Schimmenti et al., 2014; Zegers et al., 2008).

A large amount of evidence has shown that parental neglect and overcontrol, as well as poor monitoring, harsh parenting, and low parental warmth correlate with higher CU traits and psychopathy in adolescents and adults (Frick et al., 2014_b; Waller et al., 2018; Pauli et al., 2020; Trentacosta et al., 2019; Dotterer et al., 2021; O'Neill et al., 2003; Ometto et al., 2016; Schraft et al., 2013; Weiler & Widom, 1996; Gao et al., 2010; Kimbrel et al., 2007; Cima et al., 2008; Lang et al., 2002; Craparo et al., 2013; Dargis & Koenigs, 2018; Graham et al., 2012; Koivisto et al., 1996).

Furthermore, in substantiated cases of severe childhood physical abuse, sexual abuse, and neglect, processed in the county juvenile or adult criminal courts, maltreatment has been associated with CU traits (Metcalf et al., 2021; Widom et al., 2020).
Other authors believe that the role of physical abuse in promoting CU traits is more deleterious in the presence of emotional abuse, a combination labelled as "active maltreatment" more predictive of higher CU traits in children (Sharf et al., 2014; Dadds et al., 2018; Milone et al., 2019).
Emotional maltreatment has been also associated with psychopathy (Schimmenti et al., 2015).

The scientific evidence mentioned above highlights the crucial role of unsecure attachment, bad parenting and severe child maltreatment, especially physical abuse, sexual abuse, and active maltreatment, in the development of high CU traits and psychopathy. However, it is worth noting that the role of maltreatment in CU traits is still controversial and far from being completely understood. Harsh parenting and parental maltreatment, indeed, can be also elicited by CU traits (Trentacosta et al., 2019, Milone et al., 2019) suggesting a complex interplay between CU traits and negative parenting (Milone et al., 2019).

1.2.2. Biological risk factors of psychopathic traits

1.2.2.1. Neurotransmitters implicated in psychopathic traits

Alterations in the neurotransmission of the serotonergic, dopaminergic, and oxytonergic pathways have been associated with psychopathic traits, as discussed in the following paragraphs.

- Serotonergic pathway

Serotonin (5-hydroxytryptamine or 5-HT) is a biogenic monoamine, highly conserved among vertebrates. In the central nervous system (CNS), serotonergic neurons are located in the median and dorsal raphe nuclei. 5-HT plays a key role in brain development, by regulating neurogenesis, synaptogenesis, dendritic arborization, and synaptic plasticity. Serotonergic neurons are evident at week five of gestation and continue to grow, rapidly reaching the highest functional status; during the first two years of life, the 5-HT concentration continues to increase at lower rates and thereafter it starts to decline reaching

the adult levels at around five years of age (Whitaker-Azmitia, 2001; Sodhi & Sanders-Bush, 2004).

5-HT is implicated in several physiological processes, like thermoregulation, breathing, appetite, and sleep (Veenstra-VanderWeele et al., 2000; Erikson et al., 2007; Halford et al., 2012; Teran et al., 2014; Ishiwata et al., 2018), and complex functions, like mood (Lucki, 1988; Dayan & Huys,2009), sexual behavior (Hull et al., 2004; Hull & Dominguez 2007; Kiser et al., 2012), reward (Liu et al., 2014; Li et al., 2016), decision making (Homberg, 2012; McDannald, 2021), learning, and memory (Murphy et al., 2020).

Alterations of the serotonergic neurotransmission have been involved in the pathogenesis of several psychiatric disorders, including bipolar disorder, depression, anxiety, obsessive compulsive disorder, and substance abuse disorder (Coppen, 1967; Lucki, 1998). Other evidence showed that 5-HT is also implicated in the regulation of social behavior (Kiser et al. 2012). For example, reduced social behavior has been observed in mice lacking the serotonin precursor (Beis et al. 2015; Mosienko et al. 2015), while the administration of serotonin has been associated with prosocial behaviors (Schaechter & Wurtman 1990). Moreover, low concentrations of serotonin in the peripheral blood of aggressive youths have been found associated with higher CU traits (Moul et al., 2013).

Synthesis of 5-HT

5-HT is synthesized from the precursor tryptophan (Trp), which is an essential amino acid (**Figure 1.1**). The first reaction of 5-HT biosynthesis is the hydroxylation of Trp into 5-hydroxytryptophan (5-HTP) catalyzed by the tryptophan hydroxylase (TPH) enzyme, in the presence of the tetrahydrobiopterin (BH_4) cofactor. Then, an L-aromatic amino acid decarboxylase catalyzes the conversion of 5-HTP into 5-HT (Kanova & Kohout, 2021).

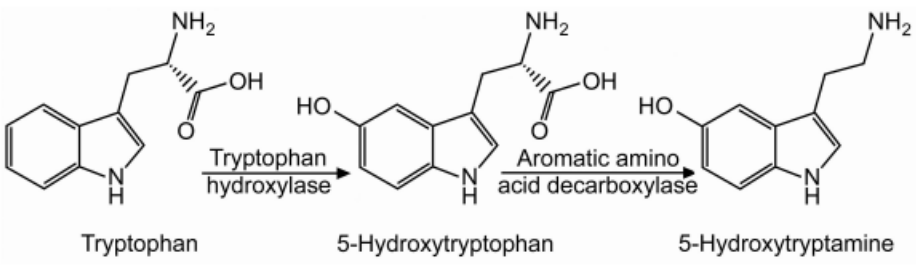

Figure 1.1. 5-HT biosynthesis. Source: Warden & Haney, 2008

The enzymatic reaction mediated by the TPH enzyme is considered rate-limiting (Noguchi et al., 1973; Tyce, 1990; Champier et al., 1997). TPH belongs to the family of protein-dependent aromatic amino acid hydroxylases (Martinez, 2001) and exists in two isoforms, TPH1 that is expressed in the periphery and in the pineal gland, and TPH2 that is expressed in the brain (Sugden, 2003).

Propagation of 5-HT signaling

5-HT is stored in the pre-synaptic vesicles of serotonergic neurons. Axonal depolarization allows the release of 5-HT in the synaptic cleft, where it interacts with specific pre- and post-synaptic receptors. Fourteen different types of 5-HT receptors (5-HTRs) have been identified, characterized by seven transmembrane domains. Except for 5-HTR3, all the other 5-HTRs are G-coupled protein receptors (GCPRs) with a Gα subunit and a dimeric Gβγ subunit. The binding of 5-HT to 5-HTRs causes conformational changes of the latter leading to a GTP/GDP substitution in Gα and the consequent activation of the receptor (Ferguson et al., 1986; Gilman, 1987; Hamm, 1998). 5-HTRs have been classified into three groups (for a review see Nichols & Nichols, 2008):

- *Gi/o-Coupled Receptor Types* (5-HT1 and 5-HT5 receptors), whose activation inhibits the adenylyl cyclase decreasing intracellular cAMP, activating membrane potassium channels, causing the hyperpolarization of 5-HT neurons.

  5-HTR1 includes the 5-HTR1A, B, D, E, and F subtypes. 5-HTR1A is found presynaptically in the raphe nuclei, where it plays a negative feedback regulation on the 5-HT release, and postsynaptically in the hippocampus, septum, and several cortical areas (Savli et al., 2012; Altieri et al., 2013). Also 5-HTR1B act both as pre-synaptic and post-synaptic receptor. Pre-synaptic 5-HTR1B is located on serotonergic neurons and regulates the release of 5-HT by negative feedback, whereas post-synaptic 5-HTR1B is located either on serotonergic or non-serotonergic neurons, such as the dopaminergic, glutamatergic, GABAergic, and acetyl-cholinergic neurons (Nichols & Nichols, 2008). 5-HTR1B is expressed in several brain areas showing the highest concentration in the globus pallidus and in the substantia nigra (Savli et al., 2012).

  The 5-HT1D, E, and F receptors are expressed in the basal ganglia, globus pallidus, substantia nigra, and hippocampus.

  The 5-HTR5 receptors include the 5-HTR5A and B subtypes, expressed in the cerebral cortex, hippocampus, nucleus accumbens, amygdala, and hypothalamus.

- *Gq/11-Coupled Receptor Types* (5-HT2 receptors), which activate the phospholipase C that produces diacylglycerol and inositol triphosphate, thus activating the protein kinase C and elevating the cytosolic concentration of calcium ions.

  5-HTR2s comprise the 5-HTR2A, B, and C, which are post-synaptic receptors located in several cortical areas and in the basal ganglia.

  5-HTR2B is highly expressed in peripheral tissues but weakly expressed in the septal nuclei, hypothalamus, and amygdala.

  Finally, the 5-HTR2C is highly expressed in the cortex, amygdala, basal ganglia, hippocampus, and thalamus.
- *Gs-Coupled Receptor Types* (5-HT4, 5-HT6, and 5-HT7 receptors), which activate adenylyl cyclases, thus leading to cAMP that regulates several cellular processes, including calcium ion flux, membrane excitability, and gene expression. 5-HTR4s are expressed in several brain regions, in particular in the putamen, caudate, and hippocampus (Beliveau et al., 2017). 5-HTR6 is a group of post-synaptic receptors highly expressed in the striatum, thalamus, hippocampus, cerebellum, nucleus accumbens, cortex, and olfactory system. Finally, the 5-HT7 receptors are expressed in the hypothalamus, thalamus, hippocampus, and cortex (Beaudet et al., 2015).

  The 5-HT3 receptors are cation ion channels, composed of five subunits surrounding a central ion-conducting pore, belonging to the Cys-loop family of receptors (Thompson &Lummis, 2007). The activation of 5-HTR3 leads to an immediate influx of extracellular calcium ions, resulting in membrane depolarization (Lummis, 2013). These receptors are expressed in the brain stem, cortical regions, olfactory tract, and forebrain (Gupta et al., 2016).

Termination of 5-HT action

5-HT is removed from the synapsis by reuptake in pre-synaptic neurons through a specific transporter, called 5-HTT (5-HT Transporter) or SERT (SErotonin Reuptake Transporter). 5-HTT is an integral membrane protein encoded by the *SLC6A4* gene, belonging to the family of sodium-dependent transporters SLC6 (Solute Carrier Family 6), which transport biogenic monoamines.

In the pre-synaptic cell, 5-HT is either stored into vesicles or degraded by specific catabolizing enzymes (Sibley, Hazelwood, & Amara, 2018). In particular, the monoamine oxidase (MAO) type A catalyzes the oxidative deamination of 5-HT in 5-hydroxy indol

acetaldehyde, which is dehydrogenated to 5-hydroxy indole acetic acid. Alternatively, an aldehyde reductase transforms 5-HT into 5-hydroxytryptol. These final products are removed from the body by renal excretion.

- **Dopaminergic pathway**

The 4 - (2 aminoethyl) benzene 1,2 diol, or dopamine (DA), is a catecholaminergic neurotransmitter. In the CNS, dopaminergic neurons are located in the substantia nigra, hypothalamus, ventral tegmental area, arcuate nucleus, paraventricular nucleus, and other hypothalamic regions. The cell bodies of dopamine neurons project to several brain areas belonging to different pathways (Baskerville & Douglas, 2010):

- The nigrostriatal pathway, where dopaminergic neurons located in the substantia nigra project to the striatum to promotevoluntary movements via the prefrontal cortex.
- The mesocortical pathway, where dopaminergic neurons located in the ventral tegmental area project to cortical regions for the regulation of emotional responses and working memory.
- The mesolimbic pathway, where dopaminergic neurons located in the ventral tegmental area project to limbic regions, including the nucleus accumbens and the amygdala, which regulate the reward system.
- The hypothalamic-derived pathway, where hypothalamic dopaminergic neurons innervate the supraoptic nucleus, paraventricular nucleus, and lateral septal nuclei, regulating endocrine functioning and sexual behavior.
- The diencephalospinal pathway, where dopaminergic neurons project from the hypothalamus to the thoracic and lumbar spinal cord, for the regulation of the spinal reflex.
- The tuberoinfundibular pathway, which connects the arcuate nucleus with the periventricular region of the hypothalamus and the median eminence for the regulation of the secretion of prolactin.

The role of dopamine in social behavior has been extensively investigated (Cairns et al., 1983; Garièpy et al., 1988; van Erp & Miczek, 2000). For example, the first studies investigating the role of DA in aggressive behavior showed higher concentrations of DA and lower density of DA receptors in aggressive mice as compared to non-aggressive ones (Lewis et al., 1988; DeVaud et al., 1989). Conversely, other studies found that, in mice,

aggressive behavior is associated with reduced expression of the enzyme involved in DA synthesis while administration of an agonist caused a reduction of aggressiveness (Popova et al., 1993; Lepicard et al., 2000).

Studies conducted in humans support the hypothesis of an association between psychopathy and increased concentrations of DA. For example, the concentration of DA in the nucleus accumbens has been found positively correlated with the socially deviant behavior of psychopathy (Buckholtz et al., 2010) and the concentration in the cerebrospinal fluid of homovanillic acid, the main metabolite of DA, has been found positively correlated with PCL-R Antisocial Lifestyle scores (Soderstrom et al., 2001, 2003).

Moreover, pharmacological and genetically driven increases of DA availability have been associated with reduced altruism and empathy (Crockett et al., 2015; Gong et al., 2014), which are core features of both CU traits (Milone et al., 2019) and psychopathy (Hare, 2003).

Synthesis of DA

DA is synthetized from the L-tyrosine (Tyr) amino acid (**Figure 1.2**). The hydrolyzation of Tyr catalyzed by the Tyrosine Hydroxylase (TH) enzyme, in the presence of the BH_4 cofactor, leads to the formation of the 3,4 dihydroxyphenylalanine (L-DOPA). Then, L-DOPA is decarboxylated in DA by an aromatic l-amino acid decarboxylase (DOPA decarboxylase) in the presence of the cofactor pyridoxal phosphate.

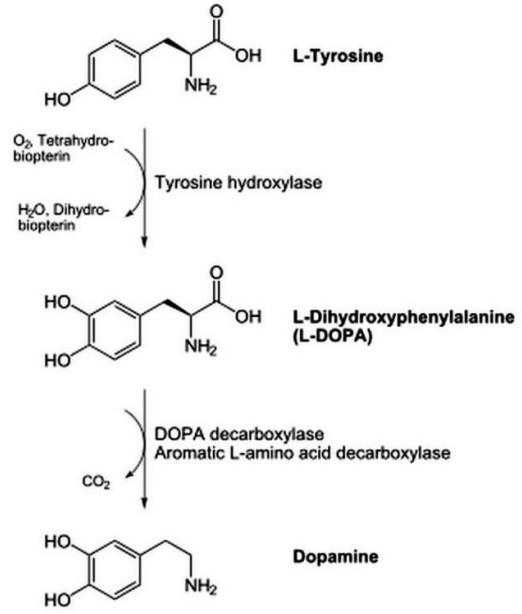

Figure 1.2. DA biosynthesis. Source: Pinoli et al., 2017

The hydroxylation of the Tyr catalyzed by TH is a rate-limiting step of the biosynthesis of dopamine. It is a member of the family of protein-dependent aromatic amino acid hydroxylases (Martinez, 2001).

In the CNS, TH is characterized by four isoforms produced by mRNA alternative splicing. The TH1 and TH2 isoforms are the most prominent in the brain.

Propagation of DA signaling

DA is stored in the pre-synaptic vesicles of dopaminergic neurons. Vesicles merge with the cell membrane when the axonal membrane is depolarized. DA is released into the synaptic cleft, where it interacts with specific DA receptors (DRs). DRs exists both as auto and hetero-receptors located both pre- and post-synaptically. There are five different DRs (DR1-5). DRs belong to the GPCR family and are grouped into two families based on their pharmacological properties and the regulation of post-synaptic cAMP concentrations:

- D1-Like receptors, including the DR1 and DR5 subfamilies, which activate the adenylyl cyclase, inducing an increase of intracellular cAMP concentration. DR1 is a post-synaptic receptor highly expressed in the nucleus accumbens, striatum, and olfactory bulb and poorely expressed in the amygdala, hippocampus, substantia nigra, and hypothalamus. D1-Like receptors modulate several ion channels, including Na^+, K^+, and Ca^{2+} channels (Maurice et al., 2001; Witkowsky et al., 2008; Yang et al., 2013).

  The DR5 receptors are characterized by a higher affinity for DA as compared to the DR1s and are expressed in the substantia nigra-pars compacta, hypothalamus, striatum, cerebral cortex, nucleus accumbens, and olfactory tubercle (Kahn et al., 2000).
- D2-Like, comprising the DR2, DR3, and DR4 subfamilies, are both pre- and post-synaptic receptors that inhibit the adenylyl cyclase with a reduction of intracellular cAMP and protein kinase A activity (Missale et al., 1998). Two isoforms of DR2 have been described: the DR2 long (DR2-L) and the DR2 short (DR2-S), generated by mRNA alternative splicing (Lindgren et al., 2003). DR2-L, as compared to the DR2-S, presents 29 additional amino acids and is primarily expressed on post-synaptic dopaminergic terminals, synergistically interacting with D1 receptors. Instead, DR2-S is a pre-synaptic auto-receptor that influences the DA release by a negative feedback regulation, while, post-synaptically, inhibits D1 receptors (Usiello et al., 2000). DR3 is expressed in the striatum, cortex, olfactory bulb, and hypothalamus (Missale et al., 1998). DR4 is a

hetero-receptor expressed in the frontal cortex, amygdala, hypothalamus, and nucleus accumbens.

Termination of DA activity

The DA transporter DAT1, encoded by the *SLC6A3* gene, removes DA from the synaptic cleft by transporting the neurotransmitter into the dopaminergic pre-synaptic terminal.
Whithin the pre-synaptic neuron, DA undergoes enzymatic degradationby the catechol-O-methyltransferase (COMT), which methylates DA into 3 methoxytyramine. DA is metabolized also by the MAO enzyme, converting DA into 3 methoxy 4 hydroxyphenylacysteine. The latter is converted into homovanillic acid by the aldehyde dehydrogenase. Alternatively, the enzyme MAO directly coverts DA into 3,4 dihydroxyphenyl acethaldehyde (DOPA-L), which is then converted into 3,4 dihydroxyphenylacetic acid (DOPA-C) by aldehyde dehydrogenase. Finally, DOPA-C is converted into homovanillic acid by COMT.

- **Oxytocinergic pathway**

Oxytocin (OXT) is a peptide hormone comprising a six-amino acid ring and a three-amino acid tail primarily synthesized in the paraventricular nuclei, supraoptic nucleus, and accessory magnocellular hypothalamic nuclei (Du Vigneaud et al., 1953).

Peripherally, OXT plays a crucial role during childbirth, by stimulating uterine contractions, and in the milk ejection reflex during lactation, by increasing the action of estrogen and promoting the contraction of myoepithelial cells of the mammary ducts (Gimpl & Fahrenholz, 2001; Donaldson & Young, 2008).

Murine studies have shown that intracerebral administration of OXT to mothers stimulated offspring care (Pedersen & Prange, 1979); on the contrary, the administration of oxytocin antagonists inhibited maternal care (Insel, 2000). Similarly, in humans, higher levels of OXT during pregnancy have been associated with better mother/child relationship (Levine et al., 2007) and intranasal administration of OXT has been associated with empathy and altruism (e.g., Palgi et al., 2015; Geng et al., 2018; Bartz et al., 2019).

Instead, lower levels of OXT have been associated with aggressive behavior (e.g., Coccaro et al., 1997; Berends et al., 2019). Nevertheless, the study by Mitchell and colleagues, which

is so far the first and only study that has investigated the urinary concentration of OXT in forensic patients with psychopathic traits (N= 47), found a positive correlation between OXT concentrations and the antisocial lifestyle dimension (Mitchell et al., 2013).

Lower concentrations of OXT in saliva (Levy et al., 2015) and peripheral blood (Dadds et al., 2014_a), as well as reduced expression of the OXT receptor (OXTR) in cord blood and peripheral blood (Cecil et al., 2014; Dadds et al., 2014_a), were observed in youths with CU traits. Conversely, childhood maltreatment has been reported to increase urinary OXT levels (Seltzer et al., 2014).

Synthesis of OXT

OXT derives from a precursor protein called pre-pro-oxytocin (Rao et al., 1992). Pre-pro-oxytocin is encoded by the *OXT/Neurophysin-I* gene, composed of three exons and two introns, located on the 20p13 chromosome. The first exon encodes a translocator signal, the nonapeptide hormone, the tripeptide processing signal (GKR), and the first 9 residues of neurophysin I; the second and third exons encode the central and carboxy-terminal regions of neurophysin I (Feldman et al., 2016) (**Figure 1.3**).

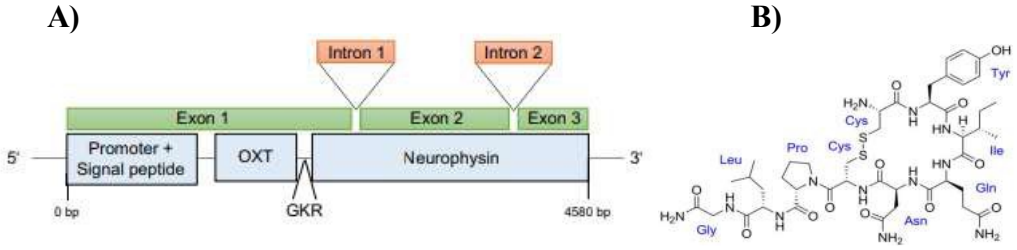

Figure 1.3. a) Schematic representation of the *OXT/Neurophysin-I* gene and b) oxytocin molecule. Jurek and Neumann, 2018.

Pre-pro-oxytocin undergoes post-translational changes and is stored in neurosecretory vesicles, where it undergoes a proteolytic cleavage that leads to the synthesis of OXT and neurophysin I (Jurek & Neumann, 2018). Then, OXT is released into the vascular system, acting on peripheral organs such as the uterine and mammary glands (Gimpl & Fahrenholz, 2001; Kirsch, 2015).

Propagation of OXT signaling

In the nervous system, OXT exerts its activity either as a local neurotransmitter or as a neuromodulator by a) diffusing into the surrounding brain tissues (Baribeau & Anagnostou,

2015; Quintana & Guastella, 2020), or b) acting on distant brain areas thanks to oxytocinergic projections to extrahypothalamic regions, such as the amygdala, ventral tegmental area, nucleus accumbens, hippocampus, cortex, brain stem, and spinal cord (Kremarik et al., 1993; Loup et al., 1991; Gimpl & Fahrenholz, 2001).

There is only one type of OXT receptor, which is encoded by the *OXTR* gene that, in humans, is located on chromosome 3p25 (Simmons et al., 1995). This gene consists of four exons and three introns: the sequence comprising exons 1 and 2 corresponds to a 5' untranslated region (UTR), while exons 3 and 4 encodethe amino acid sequence of the receptor. In addition, exon 4 contains a sequence encoding the carboxyl-terminal and the whole 3'UTR region (Gimpl and Fahrenholz, 2001).

OXTR is a 388 amino acid polypeptide with seven transmembrane domains belonging to the GPCR family (Kimura et al., 1992). Therefore, the binding of OXT to the OXTR induces a conformational change in the structure of the receptor that leads to the activation of G proteins, which lead to the phosphorylation of several intracellular proteins, the activation of nitric oxide synthase, and the modulation of gene expression (Zingg & Laporte, 2003; Baribeau & Anagnostou, 2015).

OXTR is expressed in limbic and hypothalamic structures, such as the ventromedial nucleus of the hypothalamus, hippocampus, striatum, pallidum, basolateral and central amygdala, medial preoptic area, and some cortical areas, as well as peripherally in the uterus, kidney, thymus, bones, and heart (Yoshida et al., 2009; Mitre et al., 2016; Jurek & Neumann, 2018; Newmaster et al., 2020).

1.2.2.2. Interactions among neurotransmitter pathways

In the CNS, neurons belonging to different neurochemical pathways communicate with each other and influence each other. Starting from the revision of the scientific literature, this paragraph summarizes the mechanisms by which different neurons belonging to the dopaminergic, serotonergic, and oxytocinergic pathway interact with each other.

- **Interactions between the dopaminergic and the oxytocinergic pathways**

Dopaminergic neurons express oxytocinergic receptors, especially in the ventral tegmental area (Sofroniew, 1983; Freund-Mercier et al., 1987; Vaccari et al., 1998). Furthermore, the injection of exogenous OXT in the ventral tegmental area, in the amygdala, or in the hippocampus

increases extracellular dopamine in the nuceus accumbens and in the medial prefrontal cortex; the injection of OXTR antagonists inhibited this effect (Love, 2014). The oxytocinergic neurons in the ventral tegmental area project to mesolimbic structures, including the amygdala and the nucleus accumbens (Shamay-Tsoory & Abu-Akel, 2016). The ventral tegmental area – nucleus accumbens network has been shown to be involved in social behavior and in the processing of social stimuli (Shamay-Tsoory & Abu-Akel, 2016, Peris et al., 2017; Borland et al., 2018). OXT injection, for example, increased the DA release in the nucleus accumbens and favored prosocial interactions among rats (Kohli et al., 2019). Moreover, a recent review showed that OXT promotes DA turnover in the mesocorticolimbic system, especially in the ventral tegmental area and medial preoptic area, both expressing by high levels of OXTR mRNA, increasing active maternal behavior, including pup licking and nest building (Grieb & Lobstein, 2022).

Other studies suggested that OXT has anxiolytic and anti-depressant effects and that these effects are mediated by the interaction of the oxytocinergic pathway with the dopaminergic pathway resulting in functional changes of the amygdala (Laszlo et al., 2020) and the medial prefrontal cortex (Li et al., 2020).

In addition, oxytocinergic neurons express dopaminergic receptors and, therefore, are modulated by dopamine (Baskerville et al., 2009). For example, the activation of D2 and D3 receptors in paraventricular nucleus has been shown to increase the release of OXT in this brain area (Baskerville et al., 2009).

- **Interactions between the serotonergic and the dopaminergic pathways**

Serotonergic neurons project from the raphe nuclei to mesocorticolimbic areas, like the ventral tegmental area, supraoptic nucleus, medial prefrontal cortex, and to striatal areas, like the nucleus accumbens, modulating the release of DA. The nucleus accumbens controls guilt and reward anticipation, a motivational state that promotes actions associated with the expectation of a potential reward (Knusto & Greer, 2008; Dreher & Tremblay, 2009; Apaydin et al., 2018). Increased nucleus accumbens activation, for example, has been shown to promote impulsive antisocial behavior during reward anticipation (Beck et al., 2009; Bucholtz et al., 2010) and inhibit guilt in the perspective of harming others (Chang et al., 2011). Moreover, the anterior cingulate cortex $\rightarrow$ nucleus accumbens circuit has been shown to be involved in empathic behavior (Smith et al., 2021).

Indeed, dopaminergic neurons express different subtypes of serotonin receptors (i.e., 5-HTR1A, 2A, 2C, and the 5-HTR3) (De Deurwaerdere & Di Giovanni, 2017).

Intracerebral injection of 5-HTR1A agonist or 5-HTR2A antagonist has been shown to increase the release of DA in the ventral tegmental area (Ugedo et al., 1989; Prisco et al., 1994). Dopaminergic neurons in ventral tegmental area seem to be activated by the serotonergic projections from the dorsal raphe nuclei (Nagai et al., 2020).

Ventral tegmental area activation, in turn, has been shown to stimulate the release of DA in other mesocorticolimbic regions, such as the nucleus accumbens (Wang et al., 2019; Cunha et al., 2021). Increased dopamine release in the nucleus accumbens has been observed after the administration of a Selective Serotonin Reuptake Inhibitor (SSRI) in rats (Bubar et al., 2003).

Dopaminergic neurons, instead, project to the raphe nuclei (Cai et al., 2022), in particular, the DA neurons in the ventral tegmental area project to the dorsal raphe nuclei where activate specific dopaminergic receptors expressed on the serotonergic neurons, indicating a reciprocal regulation between the serotonergic and the dopaminergic systems. DRD2 activation was shown to decrease the firing of serotonergic neuronsin the dorsal raphe nuclei, while the activation of DRD1 increased the firing (Cai et al., 2022).

Therefore, the firing of serotonergic neurons in the DRN is inhibited by D2 hetero-receptors expressed on their surface (Cai et al., 2022) and the reduced expression of these specific DRD2s may increases serotonergic signaling to mesocorticolimbic regions (Ma & Han, 1991).

- **Interactions between the serotonergic and the oxytocinergic pathways**

A bidirectional interaction between the serotonergic and the oxytocinergic pathways has been described (Grieb & Lobstein, 2022). The paraventricular nucleus and supraoptic nucleus, brain areas expressing OXTR, express also 5-HT receptors and receive serotonergic projections from the raphe nuclei (Sawchenko et al., 1983). The intracerebroventricular infusion of 5-HT has been shown to stimulate the release of OXT, especially through the action of the 5-HT1A, 5-HT2C, and 5-HT4 receptors (Jorgensen et al., 2003). On the other hand, serotonergic neurons express OXTR. More in details, about 30% of the TPH-immunoreactive cells in the dorsal raphe nuclei and about 50% in the medial raphe nuclei express OXT receptors, whose activation has been shown to stimulate 5-HT release (Yoshida et al., 2009).

Furthermore, the administration of OXT has been shown to increase the binding capacity of 5-HTR1A in the dorsal raphe nuclei (Mottolese et al., 2014). It has been hypothesized that OXT increases the release of 5-HT, and that OXT plays a crucial role in the processing of social cues through a coordinated activity with 5-HT in the mesocorticolimbic system. More in details, it has been reported that, in the dorsal raphe nuclei, the activation of the OXTRs expressed on the serotonergic projections increases 5-HT release within the nucleus accumbens, promoting social

interactions in mice (Dolen et al., 2013). The activation of these specific OXTRs has been associated with higher maternal behavior, in particular, with the nursing, aggression toward strangers, and postpartum anxiety-like behavior (Grieb & Lobstein, 2022).

1.2.2.3 Genetic risk factors of psychopathy

To date, many studies have investigated the associations between specific polymorphisms of the serotonergic, dopaminergic, and oxytocinergic pathways and different aspects of the human social behavior (Iofrida, Palumbo & Pellegrini, 2014; Fragkaki et al., 2019). Most of these association studies investigated the influence on behavior of a limited number of genetic variants selected by a candidate gene approach, while only a few of them explored the association of millions of polymorphisms by a GWAS approach, which, however, has led to non-statistically significant results (Viding et al., 2010; Viding et al., 2013).

The serotonergic, dopaminergic, and oxytocinergic genetic variants mostly investigated in association with antisocial behaviorare described below.

- **Genetic variants of the serotonergic pathway**
    - ***TPH2* rs4570625**

      rs4570625 is a G>T change in the promoter of the *TPH2* gene coding for the tryptophan hydroxylase involved in the synthesis of 5-HT. The *TPH2* rs4570625 T allele has been shown to reduce the expression of *TPH2* as compared to the C/C genotype (Chen et al., 2008). *TPH2* rs4570625 has been never studied in association with psychopathic traits; however, the T allele has been associated with reduced harm avoidance (χ^2= 10.06) (Reuter et al., 2007), a characteristic of youths with CU traits (Herpers et al., 2014). Furthermore, the same allele has been associated with higher reactivity of both right (Z= 3.02) and left (Z= 2.63) amygdala in response to fear expressions (Canli et al., 2005), as observed in aggressive subjects (da Cunha-Bang et al., 2019).

- ***5-HTR1B* rs13212041**

rs13212041 is a T>C change in the 3'UTR of the *5-HTR1B* gene. This SNP is located within a nucleotide sequence that is recognized by a microRNA (miRNA). The *5-HTR1B* rs13212041 T allele allows the binding of miRNA, resulting in an inhibition of the gene expression of *5-HTR1B* (Jensen et al., 2009; Jensen et al., 2011). The miRNA-mediated reduction of *5-HTR1B* expression is believed to be associated with decreased 5-HT reuptake and increased levels of extracellular 5-HT.

5-HTR1B rs13212041 T allele has been associated with CD (effect size (d)= 0.28) (Jensen et al., 2009), and hostility (% variance: 7.1%) (Conner et al., 2010), whereas the association with psychopathic traits was not statistically significant (Moul et al., 2013). Interestingly, the *5-HTR1B* promoter methylation has been shown to correlate with CU traits (F= 7.477, $\eta 2$= 0.178) (Moul et al., 2015).

- ***5-HTR2A* rs6314**

rs6314 is a C>T change in the third exon of the *5-HTR2A* gene, leading to a histidine to tyrosine (His/Tyr) amino acid substitution, which reduces *5-HTR2A* gene expression (Blasi et al., 2013). The *5-HTR2A* rs6314 C/C genotype has been reported as more frequent in aggressive children with high levels of CU traits (χ^2= 7.88) (Moul et al., 2013). In addition, the *5-HTR2A* rs6314 C/C genotype has been associated with rule-breaking behavior in young adults (d= 0.44) (Burt & Mikolajewski, 2008).

- **5-HTTLPR/rs25531**

5-HTTLPR (5-HTT Linked Polymorphic Region) is a variable number of tandem repeats (VNTR) consisting of 20 bp units, repeated 13-22 times, located 1kb upstream of the *SLC6A4* gene transcription start site. The most common alleles have 16 repeats, called “long” (L), and 14 repeats, called “short” (S). In particular, the 5-HTTLPR S allele, compared to the L allele, is responsible for a reduction of the gene expression and a consequent reduction of the 5-HT reuptake (Heils et al., 1996).

rs25531 is a G>A change within the *SLC6A4* VNTR described above that further influences the gene expression of 5-HTT. More in details, the presence of the *SLC6A4* rs25531 G allele in carriers of the 5-HTTLPR L allele (L_G) has been shown

to influence 5-HTT gene expression similarly to what observed in 5-HTTLPR S allele carriers (Iurescia et al., 2016). For this reason, often, the 5-HTTLPR L_G allele is referred to as 5-HTTLPR S allele.

Several studies investigated the influence of these genetic variants in association with psychopathic traits in youths and adults; however, the results are mixed. For example, some studies have shown that the 5-HTTLPR L allele is associated with CU traits in two independent samples of youths (β= -0.51 and β= -0.40, respectively) (Sadeh et al., 2010) and in another of adults (β= 1.11, standard error (SE)= 0.54) (Widom et al., 2020). Similarly, the 5-HTTLPR L allele was also associated with the emotional deficits of psychopathy (d= 0.606) (Sadeh et al., 2013), and criminal behavior (d= 0.34) (Toushchakova et al., 2017).

However, other studies have shown a significant, but weak (d= 0.085), direct association between the 5-HTTLPR S allele and CU traits (Fowler et al., 2009). Further, psychopathy has been associated with 5-HTTLPR S allele alone (β= 0.21) (Fox et al., 2020), and 5-HTTLPR/rs25531 haplotype (χ^2= 14.03) (Hollerbach et al., 2021). The 5-HTTLPR S allele has been also associated with increased vulnerability to aversive environments predisposing carriers to antisocial behavior (χ^2= 6.5) (Reif et al., 2007).

- ***MAOA* uVNTR**

The promoter of the *MAOA* gene presents a VNTR located 1.2 kb upstream of the transcription start site, called *MAOA* uVNTR, consisting of 30 bp units repeated 2, 3, 3.5, 4, and 5 times. The 2R, 3R, and 5R alleles, called "Low", have been associated with reduced *MAOA* gene expression (Sabol et al., 1998) as compared to the 3.5R and 4R alleles, called "High" (Sabol et al., 1998). The Low alleles have been associated with CU traits (d= 0.02) (Fowler et al., 2009), and psychopathy (β= 0.094) (Hollerbach et al., 2018), in particular with the antisocial/lifestyle dimension (d= 0.274) (Sadeh et al., 2013). These data are in line with previous evidence showing that the Low alleles increase the vulnerability to aversive experiences, for example making carriers exposed to maltreatment more susceptible to violent antisocial behavior (OR= 9.8, 95% CI: 3.10 to 31.15) (Caspi et al., 2002).

Conversely, a recent study has found a significantrelation between the MAOA High alleles and the antisocial/lifestyle dimension of psychopathy (β= -0.11) (Fox et al., 2020).

- **Genetic variants of the dopaminergic pathway**
  - ***TH* rs6356**

rs6356 is a G>A change in the second exon of the *TH* gene, which causes a valine to methionine (Val/Met) amino acid substitution (Lüdecke & Bartholomé, 1995).The specific functional effect of this SNP is still unknown; however, the Genotype-Tissue Expression (GTEx) database, collecting tissue-specific effects of genetic polymorphisms on the gene expression in 54 different tissues from about 1000 healthy individuals, showed that the A/A genotype is significantly associated with a higher expression of *TH* (OR= 0.29-0.40) in post-mortem skin samples (https://gtexportal.org/home/snp/rs6356), while similar, but not significant, trends have been observed in several brain regions.

TH rs6356 has never been investigated before in association with psychopathic traits and behavior, however its association with alcohol abuse has been described (OR = 1.988, 95% CI: 1.006–3.930) (Celorrio et al., 2012), and other evidence has shown that alcohol abuse is often observed in people with CU traits or psychopathy (Craig et al., 2021).

  - ***ANKK1* rs1800497**

rs1800497 is a C>T change (also called A2>A1) in the *ankyrin repeat and kinase domain containing 1* (*ANKK1*) gene coding for a protein kinase enzyme involved in the regulation of the D2 receptor availability. The C>T change causes a glutamate to lysine (Glu/Lys) amino acid substitution in a putative binding domain of ANKK1. The presence of the T allele has been associated with lower density of presynaptic inhibitory DR2s and higher DA availability in the striatum (Ritchie & Noble, 2003; Savitz et al., 2013; Eisenstein et al., 2016). Moreover, the *ANKK1* rs1800497 T allele has been shown to promote the uptake of the DA precursor L-DOPA by the striatum (Laakso et al., 2005), hypothesized to reflect a higher activity of the aromatic L-amino acid decarboxylase, which is the final enzyme in the biosynthesis of DA, thus consequently increasing DA synthesis (Laakso et al., 2005).

The *ANKK1* rs1800497 T allele has been associated with cannabis assumption (χ^2= 6.424) (Vereczkei et al., 2022) and alcoholism (d= 1.19) (Wang et al., 2013). Furthermore, it has been shown that the *ANKK1* rs1800497 T allele characterizes individual with high levels of psychopathy (β= 0.68, SE= 0.33) (Wu et al., 2013), and interpersonal/affective deficits (F= 7.291, R^2= 0.053) (Hoenicka et al., 2007). In addition, this allele was more frequent in aggressive children (OR= 1.66; 95% CI: 1.11–2.50) (Zai et al., 2012) and suicide attempters (d= 1.2) (Genis-Mendoza et al., 2017) and was predictive of CD (b= 0.322, SE= 0.15) and antiscocial behavior (b= 0.656, SE= 0.23) in interaction with a polymorphism of *DRD4* gene (Beaver et al., 2007).

Moreover, the *ANKK1* rs1800497 T allele seems to interact with negative parenting making carriers more susceptible to cognitive and attentive impulsivity (χ^2= 13.178) (Palumbo et al., 2022_b).

- ***DRD4* exonIII VNTR**

In the third exon of the *DRD4* gene there is a VNTR characterized 48 bp units, repeated 1-11 times (Chang et al., 1996). *DRD4* gene expression and DA binding efficiency have been shown to be higher in carriers of the shorter alleles, as compared to carriers of the longer alleles (Simpson et al., 2010; Jovanovic et al., 1999).

The 7R allele has been associated with psychopathy in adults (β= 1.00, SE= 0.38) (Wu et al., 2013) and in adolescents exposed to low maternal care (β = −0.226) (Nikitopoulos et al., 2014).

Furthermore, the *DRD4* 7R allele has been associated with CD (b= 0.322, SE= 0.15), antisocial behavior (b= 0.656, SE= 0.23) (Beaver et al., 2007), and substance abuse (OR= 5.20, 95% CI: 1.42–19.04) (Mallard et al., 2016). Moreover, the 5R and longer alleles have been associated with serious crimes (OR= 4.37; 95% CI: 2.4–7.8), such as felonies (Cherepkova et al., 2019).

The 7R allele appears to increase the sensitivity to negative parenting (King et al., 2016). For example, it has been shown that the exposure to prenatal maternal stress makes carriers of the 7R allele more susceptible to externalizing behaviors in

childhood (β= -0.246) (King et al., 2016) and aggressive behavior in adulthood (β= 0.487) (Buchmann et al., 2014).

- ***DRD4* rs1800955**

rs1800955 is a C>T change in the 5'-promoter region of the *DRD4* gene. The *DRD4* rs1800955 T allele has been shown to decrease by 40% the transcriptional efficiency of *DRD4* (Okuyama et al., 1999).

No studies have ever investigated this polymorphism in association with psychopathic traits; however, the *DRD4*rs1800955 T/T genotype has been associated with ADHD (χ^2= 6.22) (Yang et al., 2008).

- **DAT1 3'UTR VNTR**

In the 3'UTR of the *SLC6A3* gene there is a VNTR region known as DAT1 3'UTR VNTR consisting of 40 bp repeated units. The functional effect of this polymorphism is conflicting. Indeed, higher DAT1-binding capacities have been associated with both the 10R allele (Heinz et al., 2000; VanNess et al., 2005) and the 9R allele (Jacobsen et al., 2000; van Dyck et al., 2005). Moreover, a more recent study found no significant effect of this polymorphism on the transporter availability (Jakobson Mo et al., 2022).

Two studies showed non-significant effect this polymorphism on psychopathic traits (Hoenicka et al., 2007; Wu et al., 2013). Nevertheless, the 10R/10R genotype has been associated with criminal behavior (OR= 2.85; 95% CI: 1.35-5.59) and drug abuse (OR= 1.758, 95% CI= 1.026–3.012) (Cherepkova et al., 2016; Stolf et al., 2014). Further, a recent meta-analysis found an association between the 10R allele and ADHD (OR= 1.1301, 95% CI: 1.0316 -1.2379) (Grünblatt et al., 2019).

Of note, in adolescents carrying the 10R allele, the risk of rule-breaking behavior was highest if they were exposed to peer rejection (β= 0.25), and lowest in the absence of peer rejection (Janssens et al., 2015).

- ***COMT* rs4680**

rs4680 is a G>A change in the *COMT* gene causing a valine to methionine (Val>Met) amino acid substitution in position 158. The Met allele has been

associated with a 25% reduction of the enzymatic activity of COMT, which in turn leads to a higher DA availability (Strous et al., 1997; Männistö & Kaakkola, 1999; Chen et al., 2004).

The *COMT* rs4680 G allele has been associated with CU traits in adolescents (d= 0.082) (Fowler et al., 2009); however, this association was not significant in the study of Hirata and colleagues (Hirata et al., 2013) probably due to the fact that the effect size was small.

The *COMT* rs4680 G/G genotype has been associated with antisocial behavior in three independent samples of ADHD children (d= 0.32) (Caspi et al., 2008) and with CD in adolescents (χ^2= 11.08) (DeYoung et al., 2010). Moreover, ADHD subjects carrying the Val/Val genotype were more likely to have been convicted for a crime (OR= 2.3, 95% CI= 1.3-4.2) (Caspi et al., 2008).

Prenatal exposure to stress in carriers of the *COMT* rs4680 G/G genotype has been shown to be an even better predictor of aggressive behavior in adolescence (β= 0.14) and adulthood (β= 0.11) (Brennan et al., 2011). Similarly, the exposure to stress seems to make children with the same genotype significantly more aggressive (b= -1.33, 95% CI: 2.23-0.43) than A allele carriers (Hygen et al., 2015).

However, other studies showed significant modest associations between the A allele and aggression (β= 0.146) and anger (β= −0.17) (Albaugh et al., 2010; Oppenheimer et al., 2013). Stronger associations emerged between the *COMT* rs4680 A/A genotype and novelty-seeking (d= 0.47) (Scacchia et al., 2021), and drinking problems (d= 0.73) (Guillot et al., 2015).

- **Genetic variants of the oxytocinergic pathway**
  - ***OXTR* rs53576**

rs53576 is a A>G change in the third intron of the *OXTR* gene. The functional effect of this SNP is not known, however, the GTEx database shows that the *OXTR* rs53576 A allele is significantly associated with increased expression of OXTR mRNA in several brain regions, such as the caudate (OR= -0.54), nucleus accumbens (OR= -0.50), cortex (OR= -0.47), putamen (OR= -0.45), frontal cortex (OR= -0.43), and hippocampus (OR= -0.41) (https://gtexportal.org/home/snp/rs53576). The same allele has been associated with CU traits in children(OR= 3.81, 95% CI: 1.05-13.87)

(Ezpeleta et al., 2019). Higher levels of physical aggression (F= 5.509, η^2= 0.029) and hostility (F= 6.443, η^2= 0.033) have been also observed in adolescents with a history of stressful life events if carriers of the OXTR rs53576 A/A genotype (Shao et al., 2018).

Moreover, incarcerated adults with the *OXTR* rs53576 A/A genotype had higher levels of psychopathy compared to those with A/G (d= 0.36) or G/G (d= 0.49) genotype, especially the affective (A/A vs A/G: d= 0.43, A/A vs G/G: d= 0.56) and lifestyle (A/A vs A/G: d= 0.53, A/A vs G/G: d= 0.57) domains (Verona et al., 2018). These data are in line with a recent meta-analysis showing that adults with the *OXTR* rs53576 G allele have slightly increased empathic abilities (d= 0.17) than carriers of the A/A genotype (Chander et al., 2021). These data contrast with a study showing significant associations between the *OXTR* rs53576 G allele and anger and hostility (Butovskaya et al., 2020), even if the size of the effects was small (anger: d= 0.26, hostility: d= 0.28).

- ***OXTR* rs1042778**

rs1042778 is a G>T change in the 3'UTR of the fourth exon of the *OXTR* gene. Lower plasma OXT levels characterize carriers of the *OXTR* rs1042778 T/T genotype compared to *OXTR* rs1042778 G allele carriers (Feldman et al., 2012).

Bioinformatics analyses predicted that this SNP is located in the binding site of the transcription factor MAZ (Myc Associated Zinc-finger protein), which is involved in the start and termination of the transcription of *OXTR*, and that the *OXTR* rs1042778 G allele allows the binding of MAZ (de Oliveira Pereira Ribeiro et al., 2018).

The *OXTR* rs1042778 T/T genotype has been associated with CU traits in two independent samples of youths with CD (d= 0.292 and d= 0.415, respectively) (Dadds et al., 2014$_b$). However, a previous study found no significant association between *OXTR* rs1042778 and CU traits (Malik et al., 2012).

Furthermore, the *OXTR* rs1042778 T allele has been associated with enhanced reactivity of the right amygdala in response to angry facial expressions (β= 0.15), which, in turn, has been linked to antisocial behavior (Waller, Corral-Fríaset al., 2016).

- ***OXTR* rs237885**

rs237885 is a T>G change in the third intron of the *OXTR* gene with unknown functional effect.

The *OXTR* rs237885 T/T genotype has been associated with CU traits in aggressive children (β= 0.256) (Beitchman et al., 2012) and with aggressive behavior in subjects with a childhood history of physical abuse (OR=1.40, 95% CI, 1.04–1.89) (Zhang et al., 2018). However, other studies showed no significant effects of *OXTR* rs237885 on aggressiveness (Malik et al., 2014) and CD (Sakai et al., 2012) in youths.

Aim of the study

My Ph.D. project was part of a larger research program aimed at studying the molecular and environmental correlates of antisocial behavior. This program started a few years ago as a collaborative study among the University of Pisa, the University of New Mexico (Albuquerque, NM, USA) and the Stella Maris Foundation (Pisa, Italy).

Specifically, my PhD work focused on the investigation of the genetic and environmental correlates of psychopathy from childhood to adulthood with the aim of identifying genetic biomarkers that could be early predictors of psychopathy and that might improve the rate of success in preventing youths with conduct disorder (CD) to develop psychopathy as adults. Youths with early-onset CD, indeed, are known to be at risk of developing life-course-persistent antisocial problems (Odgers et al., 2008).

In details, 14 polymorphisms belonging to the serotonergic (*5-HTR1B* rs13212041, *5-HTR2A* rs6314, *MAOA* uVNTR, 5-HTTLPR, *TPH2* rs4570625), dopaminergic (*ANKK1* rs1800497, *COMT* rs4680, *DRD4* exonIII VNTR, *DRD4* rs1800955, *TH* rs6356, *SLC6A3* 40bp VNTR), and oxytocinergic (*OXTR* rs53576, rs1042778, rs237885) pathways, for which most evidence exists in the scientific literature regarding their association with antisocial behavior, were genotyped in three groups of subjects, each of which representative of a different age of life:

a) 985 White male incarcerated adults (19-65 years old) that are the largest sample of criminals studied so far;

b) 180 White male incarcerated adolescents (14-18 years old);

c) 120 White male youths with Conduct Disorder (CD) (7-16 years old).

Both sample a and b were recruited from US prisons by Prof. Kent Kiehl of the University of New Mexico, while the sample c was enrolled at IRCCS Stella Maris Foundation, Pisa, Italy,by Dr. Pietro Muratori.

Psychopathic traits were assessed in incarcerated adults by the Psychopathy Checklist-Revised (PCL-R) questionnaire, in incarcerated adolescent by the Psychopathy Checklist:Youth Version (PCL:YV), and in CD youths by the Antisocial Process Screening Device (APSD). Youths were also assessed for Callous-Unemotional (CU) traits by the APSD-CU subscale, as CU traits may be anticipative of the adult affective dimension of psychopathy.

Finally, in a subgroup of 247 incarcerated adults, the *Measure of Parental Style* (MOPS) questionnaire was used to measure the perceived behavior of their parents during the first 16 years of life, while, in CD youths, maltreatment data were collected by the Maltreatment Index (MI) scale. Environmental data were not available for the incarcerated adolescents.

Chapter 3

Materials and methods

3.1 Study participants

The study includedthree samples:

- 985 US White male incarcerated adults (19-65 years old) from The Mind Research Network cohort (Albuquerque, NM, USA) recruited by Professor Kent Kiehl (University of New Mexico) at New Mexico and Wisconsin facilities.
- 180 US White male incarcerated adolescents (14-18 years old) from The Mind Research Network cohort (Albuquerque, NM, USA) recruited by Professor Kent Kiehl (University of New Mexico) at New Mexico and Wisconsin facilities.
- 120 Italian White male youth patients (7-16 years old) with diagnosis of Conduct Disorder (CD) enrolled at IRCCS Stella Maris Foundation, Pisa (Italy).

Intelligent quotient (IQ) was estimated by using the Wechsler Adult Intelligence Scale (WAIS 3rd Edition) in the Mind Research Network cohort and the Wechsler Intelligence Scale for Children (WISC 4th edition) in the CD youth cohort.

See **Table 3.1.** for demographics related to race, ethnicity, gender, age, and IQ.

Sample	N	Race	Ethnicity	Gender	Age (mean ± SD)	IQ (mean ± SD)
Incarcerated adults	985	White	539 not-Latin/Hispanic	Male	34.65 ± 9.64	98.20 ± 13.44
			446 Latin/Hispanic			
Incarcerated adolescents	180	White	44 not-Latin/Hispanic	Male	17.02 ± 1.12	92.05 ± 12.96
			136 Latin/Hispanic			
CD youths	120	White	120 Caucasian	Male	9.46 ± 1.75	99.78 ± 8.64

Table 3.1.Demographics. CD= Conduct Disorder, IQ= Intelligence Quotient, SD= Standard Deviation.

Research was carried out in compliance with ethical standards and in accordance with the International Ethical Guidelines of the Declaration of Helsinki.

The study was approved by the IRB Ethical and Independent Review Services (E&I), the University of New Mexico Health Science Center IRB and the IRCCS Stella Maris Foundation local ethical committee.

Each participant from the Mind Research Network cohort provided a written informed consent to participate to the study.

Concerning the IRCCS Stella Maris Foundation cohort, written consents were obtained from parents/guardians of each enrolled child, after being informed about the study by the clinicians.

Subjects could withdraw from the study at any time.

3.2 Assessment of psychopathic traits

3.2.1 *Psychopathy Checklist–Revised (PCL-R)*

Psychopathic traits of incarcerated adults were measured by the PCL-R, a 20-item questionnaire based on a semi-structured interview with 125 questions (see **Appendix A** for a complete version of the questionnaire) (Hare, 2003).

Eighteen items can be grouped into two subscales (Hare & Neumann, 2009):

- PCL-R Factor 1, to evaluate the interpersonal/affective dimension of psychopathy:
    - Interpersonal (Facet 1, four items): glibness/superficial charm, grandiose sense of self-worth, pathological lying, conning/manipulative.
    - Affective (Facet 2, four items): lack of remorse or guilt, shallow affect, callous/lack of empathy, failure to accept responsibility.
- PCL-R Factor 2, to assess the developmental course of lifestyle/antisocial tendencies:
    - Lifestyle (Facet 3, five items): need for stimulation, parasitic lifestyle, lack of realistic long-term goals, impulsivity, irresponsibility.
    - Antisocial (Facet 4, five items): poor behavioral control, early behavioral problems, juvenile delinquency, revocation of conditional release, criminal versatility.

The two items not included in the two factors assess the presence of promiscuous sexual behavior and many short-term relationships, respectively.

Each item was rated by the clinician on a 3-point Likert scale ("0"= the item does not apply to the subject; "1"= the item partially applies to the subject; "2"= the item completely applies to the subject).

A total score, ranging from 0 to 40, was calculated, reflecting the degree up to which a person embodies the prototypical profile of a psychopath. Scores equal or higher of 30 are suggestive of psychopathy, whereas scores equal or below 22 indicate the absence of psychopathic traits (Sample & Smyth, 2005; Skeem et al., 2011). Moreover, scores were computed for the two subscales separately, ranging from 0 to 16 for PCL-R Factor 1 and from 0 to 20 for PCL-R Factor 2.

3.2.2 *Psychopathy Checklist:Youth Version (PCL:YV)*

Psychopathic traits of incarcerated adolescents were measured by the PCL:YV, a 20-item questionnaire based on a semi-structured interview with 125 questions (see **Appendix B** for a complete version of the questionnaire) (Hare, 2003).

The 20 items can be grouped into two subscales (Hare & Neumann, 2009):

- PCL:YV Factor 1, to evaluate the interpersonal/affective dimension of psychopathy:
    - Interpersonal (Facet 1, four items): glibness/superficial charm, grandiose sense of self-worth, pathological lying, conning/manipulative.
    - Affective (Facet 2, fouritems): lack of remorse or guilt, shallow affect, callous/lack of empathy, failure to accept responsibility for own actions.
- PCL:YV Factor 2, to assess the developmental course of behavioral/antisocial tendencies:
    - Behavioral (Facet 3, five items): need for stimulation/proneness to boredom, parasitic lifestyle, lack of realistic and long-term goals, impulsivity, irresponsibility.
    - Antisocial (Facet 4, five items): poor behavioral control, early behavioral problems, juvenile delinquency, revocation of conditional release, criminal versatility.

Each item was rated by the clinician on a 3-point Likert scale ("0"= the item does not apply to the subject; "1"= the item partially applies to the subject; "2"= the item completely applies to the subject).

A total score, ranging from 0 to 40, was calculated with higher scores indicating greater psychopathic personality; however, the scientific literature does not suggest a cut-off score for PCL:YV as diagnostic criteria are defined only for adults. Moreover, scores were computed for the

two subscales separately, ranging from 0 to 16 for PCL:YV Factor 1 and from 0 to 20 for PCL:YV Factor 2.

3.2.3 *Antisocial Process Screening Device (APSD)*

Psychopathic traits of CD youths were measured by the APSD, a 20-item parent-report questionnaire (see **Appendix C** for a complete version of the questionnaire) comprising 18 items that can be grouped into three subscales for the evaluation of the interpersonal, affective and antisocial/lifestyle dimensions, respectively (Frick, 2001):

- Narcissism, for the assessment ofthe interpersonal dimension by seven items: emotions are fake, brags about abilities, cons othersto get what you want, teases/makes fun of others, acts charming to get things, gets angry when corrected, thinks to be more important than others.
- Callous unemotional (CU) traits, for the assessment of the affective dimension by six items: cares about schoolwork*, good at keeping promises*, feels bad when do something wrong*, concerned about others' feelings, hides feelings from others, keeps same friends*. *items are reverse scored.
- Impulsiveness, for the assessment of the behavioral/lifestyle dimension by five items: blames others for mistakes, acts without thinking, gets bored easily, does risky things, does not plan ahead.

The two items not included in any of the three subscales assess engaging in illegal activities and lying easily, respectively.

Each item wasrated on a 3-point Likertscale (0= never true, 1= sometimes true, or 2= often true). A total score, ranging between 0 and 36 was calculated, by obtaining the sum of the scores of each subscale, thus not including then engaging in illegal activities and lying easily. Higher scores indicate greater psychopathic traits. Moreover, because CU traits in the presence of conduct disorder seem to predict higher risk for later psychopathy (Burke et al., 2007; Hawes et al., 2017), a score ranging from 0 to 12 was calculated for the CU traits subscale (APSD-CU). For the latter, a cut-off of sixis suggestive of the presence of CU traits, as indicated in the APSD manual.

3.3. Assessment of aversive family environment

Data about aversive family environment were collected both in a subgroup of the incarcerated adults and in youths with CD. Data about the family environment were not available for the group of incarcerated adolescents.

3.3.1. Measure of Parental Styles (MOPS)

In a subsample of 247 incarcerated adults, perceived parenting was assessed by MOPS (Parker et al., 1997), a self-report questionnaire measuring three aspects of the parenting experienced during the first 16 years of life by using 15 items for each parent (see **Appendix D** for a complete version of the questionnaire):

- Indifference, measured by six items: ignored, rejected, left alone for a long time, uncaring parents, uninterested parents, parents would forget about their child.
- Over-control, measured by four items: overprotective parents, over-controlling parents, feeling blamed, feeling criticized.
- Abuse, measured by five items: verbally abused, physically abused, feeling in danger, feeling unsafe, unpredictable parents.

Each item was rated on a 4-point Likert scale indicating the degree to which each item applies to the subject (0= not true at all; 1= slightly true; 2= moderately true; 3= extremely true).
For each parent, a total score ranging from 0 and 45 was calculated. Higher scores indicated a more dysfunctional parenting.

3.3.2. Maltreatment Index (MI)

In youths with CD, maltreatment was evaluated by the MI questionnaire (Dadds et al., 2018), a clinical-report interview based on the Maltreatment Classification System (Barnett et al., 1993) measuring three types of childhood maltreatment (see **Appendix E** for a complete version of the questionnaire):

- Emotional abuse, evaluating the infliction of insults, humiliation and behaviors that instill fear in the child such as: being belittled or ridiculed, fear or intimidation, being blamed inappropriately, extreme negativity and hostility, exposure to violence, abandonment, being confined in an enclosed space, threats of violence.

- Physical abuse, evaluating non-accidental infliction of physical injury to the child, ranging from mild and temporary to permanent and disfiguring: being hit, being bruised, being choked, being burnt, having bones broken.
- Neglect, evaluating the failure to pay inadequate attention to basic physical needs of the child, the lack of supervision, moral/legal neglect, and education neglect: being left without supervision, not being given enough to eat, not having enough clothing and/or shelter, not having enough medical treatment, being exposed to weapons, being left in the care of dangerous people, being exposed to criminal activity, not being sent to school.

Each item was rated by using a 4-point Likert scale indicating the degree to which each item was true (1= never; 2= a little bit; 3= a fair bit; 4= all the time).

A total score between 3 and 12 was calculated. Higher scores reflect greater emotional abuse, physical abuse, and neglect. Moreover, because active maltreatment was previously shown to play a crucial role in the development of CU traits (Sharf et al., 2014), active maltreatment was calculated by combining the score obtained at the Emotional subscale together with the score obtained at the Physical Abuse subscale (Dadds et al., 2018).

3.4. Collection of saliva samples

Each participant donated a sample of saliva by an ORAGENE collection tube (DNA OG-500; DNA Genotek Inc., Ontario, Canada). All subjects were asked to avoid smoking, drinking, and eatingat least 30 minutes before the collection. Sampling was performed by following the protocol provided by the manufacturing company (**Figure 3.1**).

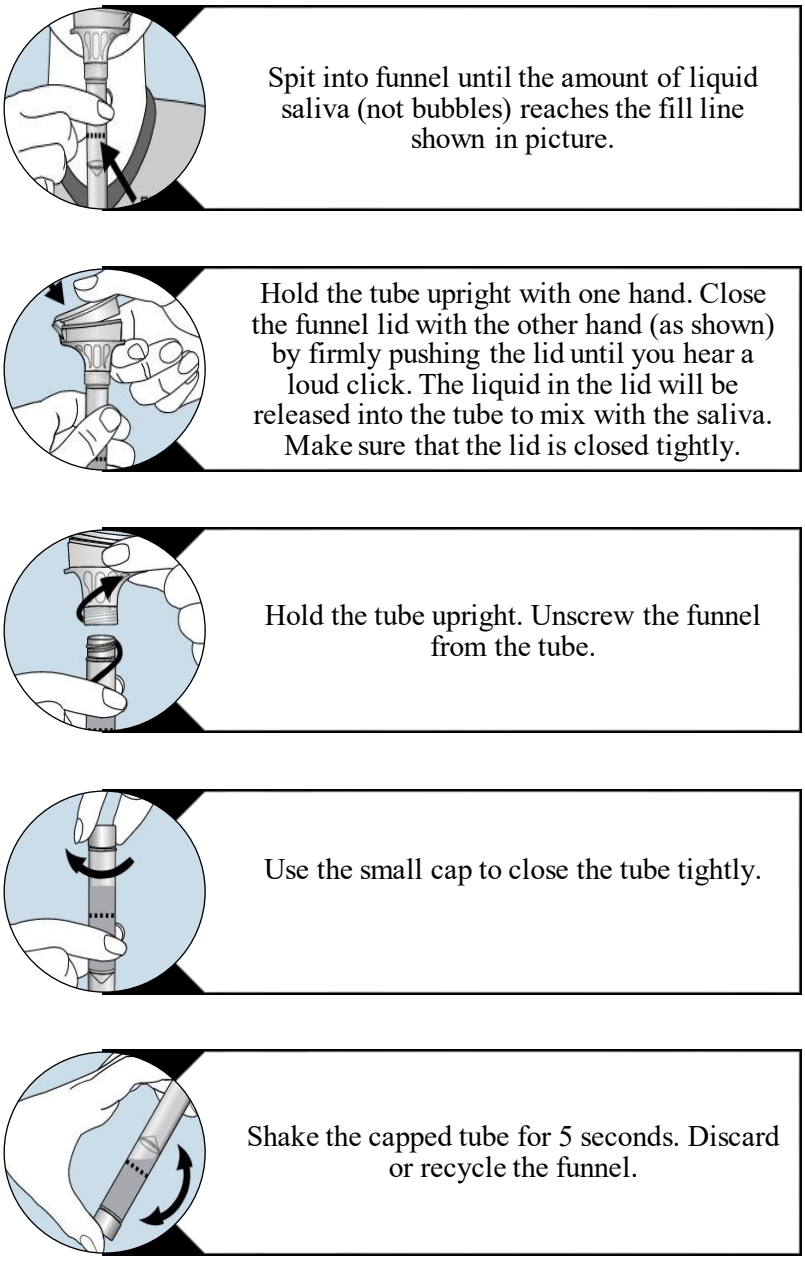

Figure 3.1. Procedure for saliva collection into ORAGENE tubes (DNA OG-50, DNA Genotek Inc.).

The tube contains a stabilizing solution to preserve DNA at room temperature for a long time.

3.5. DNA extraction

The DNA was extracted from saliva by using the prepITL2P kit (DNA Genotek Inc.) following the manufacturer's protocol:

- Incubate the sample at 50°C in a water incubator for a minimum of 1 hour or in an air incubator for a minimum of 2 hours. This step is essential to ensure the release of DNA and the permanent inactivation of nucleases.
- Transfer 500 µl of the mixed sample to a 1.5 ml tube.
- Add 20 µl of PT-L2P to the tube and mix by vortexing for a few seconds. The sample will become turbid as impurities and inhibitors are precipitated.
- Incubate in ice for 10 minutes.
- Centrifuge at room temperature for 5 minutes at 13000 rpm.
- Carefully transfer the clear supernatant into a fresh tube. Discard the pellet containing impurities.
- To 500 µl of supernatant, add 600 µl of room temperature 100% ethanol. Mix gently by inversion 10 times.
- Allow the sample to stand at room temperature for 10 minutes to allow the DNA to fully precipitate.
- Centrifuge at room temperature for 2 minutes at 13000 rpm.
- Carefully remove the supernatant with a pipette and discard it. Take care to avoid disturbing DNA pellet.
- Ethanol wash: carefully add 250 µl of 70% ethanol, let stand at room temperature for 1 minute. Completely remove the ethanol without disturbing the pellet. Carry over of ethanol may impact the performance of the assay.
- Add 100 µl of water to dissolve the DNA pellet and vortex for at least 5 seconds.
- Incubate at 50°C for 1 hour to ensure the complete rehydration of the DNA.

DNA integrity was evaluated by running electrophoresis on a 1% agarose gel containing ethidium bromide. Ethidium bromide intercalates into the DNA and fluoresces under UV light allowing the visualization of fluorescent bands. A single compact band represents DNA integrity (**Figure 3.2**).

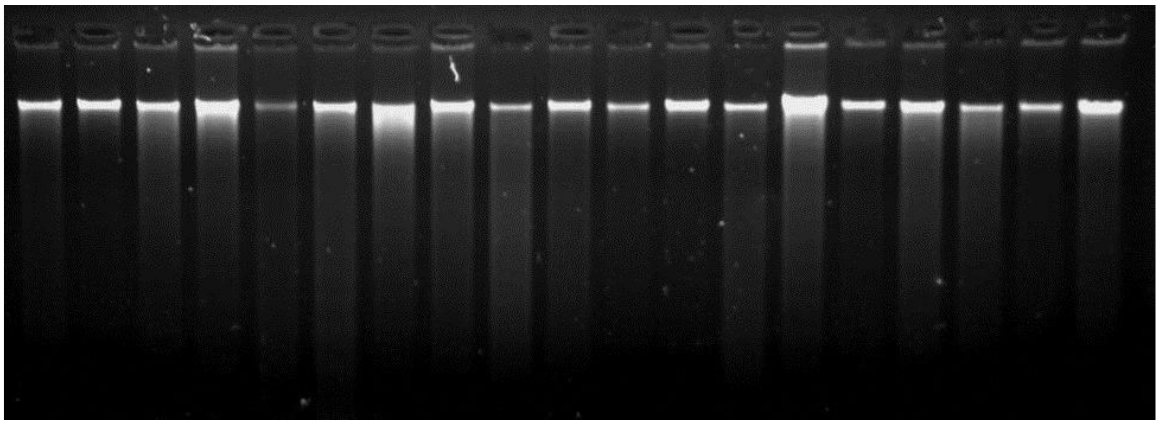

Figure 3.2. Representative DNA samples visualized on a 1% agarose gel.

The quantity and quality of the extracted DNA were evaluated by the spectrophotometer Nanodrop®ND-1000 (Thermo-Fisher Scientific, Waltham, MA, USA) (**Figure 3.3**). To calculate DNA quantity, absorbance readings were performed at 260 nm. Contamination from proteins was evaluated by calculating the ratio of absorbances (A) at 260 and 280 nm, and contamination from other organic compounds was assessed by the ratio of absorbances at 260 and 230 nm. Good-quality DNA is commonly characterized by a A_{260}/A_{280} ratio equal or higher than 1.8, and a A_{260}/A_{230} ratio equal or higher than 2.0 (Thermo-Fisher Scientific).

Figure 3.3. Nanodrop®ND-1000 (Thermo-Fisher Scientific) spectrophotometer.

3.6. Genotyping

3.6.1. Polymerase Chain Reaction (PCR) followed by electrophoresis

DNA fragments containing the polymorphisms were amplified by PCR using a 2X mastermix containing One Taq GC reaction Buffer (promoting the amplification of sequences rich in CGs), Taq-polymerase enzyme, dNTPs mix solution (400µM), ultrapure H_2O, and One Taq High Enhancer Buffer (only to genotype the *DRD4* exonIII VNTR) (New England Biolabs Inc., Ipswich, MA, USA).

PCR products were separated by electrophoresis on a 2% agarose gel, stained with ethidium bromide, together with a reference ladder with a resolution of 50bp (GeneRuler DNA ladder, Thermo-Fisher Scientific).

- ***SLC6A3* 3'UTR VNTR**
  Reaction mix:

Reagent	Final concentration
Master mix 2X	1X
Primer forward: TGTGGTGTAGGGAACGGCCTGAG	0.1 µM
Primer Reverse: CTTCCTGGAGGTCACGGCTCAAGG	0.1 µM
DNA	2.4 ng/µl
H_2O	Up to 10 µl

PCR protocol:

DNA polymerase activation	4 min	94°C	
DNA denaturation	30 sec	94°C	35 cycles
Primers annealing	1 min	62°C	
Extension	1 min	68°C	
Final extension	5 min	68°C	
Hold	∞	12°C	

SLC6A3 3'UTR VNTR is characterized by seven possible alleles, leading to the separation of the following amplicons (**Figure 3.4**):

Amplicons (R= repeats)	Length
3 R	200bp
6 R	320bp
8 R	400bp
9 R	440bp
10 R	480bp
11 R	520bp
12 R	560bp

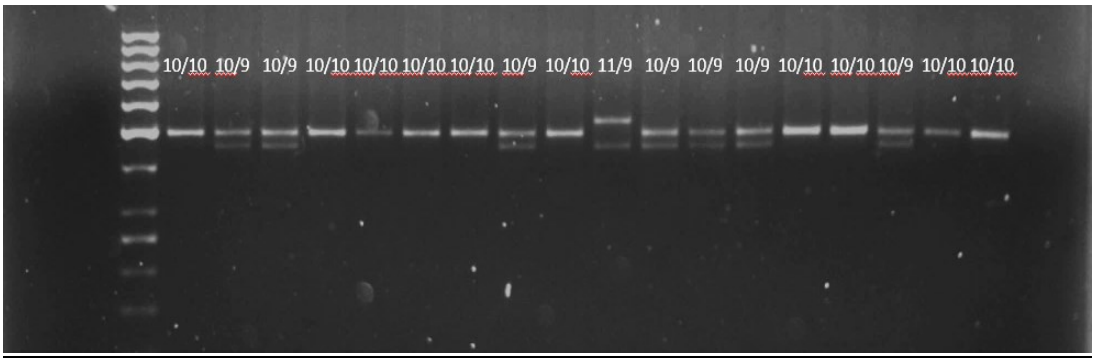

Figure 3.4. *SLC6A3* 3'UTR VNTR amplicons visualized on a 2% agarose gel.

DRD4 exonIII VNTR

Reaction mix:

Reagent	Final concentration
Master mix 2X	1X
Primerforward: CGTTGCCGCTCTGAATGC	0.1 µM
Primerreverse: GGGAGATCCTGGGAGAGGT	0.1 µM
One Taq High Enhancer Buffer	5%
DNA	2.4 ng/µl
H_2O	up to 10 µl

PCR protocol:

DNA polymerase activation	4 min	94°C	
DNA denaturation	30 sec	94°C	40 cycles
Primers annealing	1 min	60°C	
Extension	1 min	68°C	
Final extension	5 min	68°C	
Hold	∞	12°C	

DRD4 exonIII VNTR is characterized by eleven possible alleles, leading to the separation of the following amplicons (**Figure 3.5**):

Amplicons (R= repeats)	Length
1 R	326bp
2 R	374bp
3 R	422bp
4 R	470bp
5 R	518bp
6 R	566bp
7 R	614bp
8 R	662bp
9 R	710bp
10 R	758bp
11 R	806bp

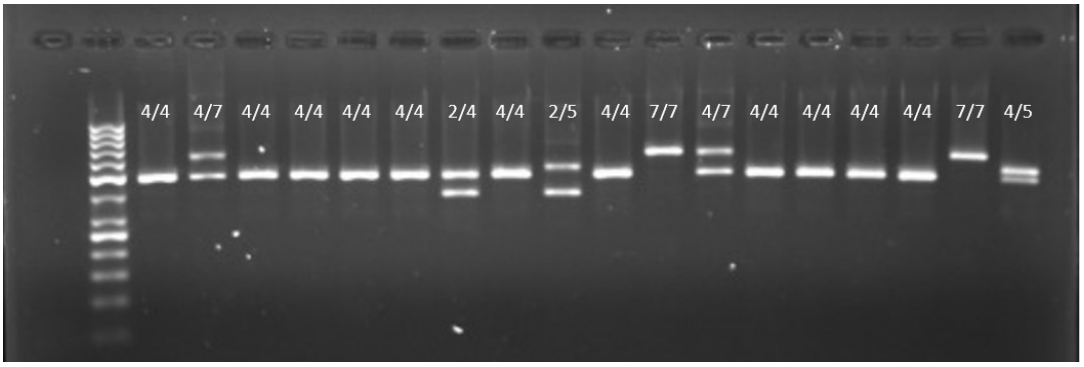

Figure 3.5. *DRD4* exonIII VNTR amplicons visualized on a 2% agarose gel.

- ***MAOA* uVNTR**

Reaction mix:

Reagent	Final concentration
Master mix 2x	1x
Primer forward: ACAGCCTGACCGTGGAGAAG (Sabol et al., 1998)	0.2 µM
Primer reverse: GAACGGACGCTCCATTCGGA (Sabol et al., 1998)	0.2 µM
DNA	2.5 ng/µl
H_2O	Up to 20 µl

PCR protocol:

DNA polymerase activation	4 min	94°C	
DNA denaturation	30 sec	94°C	35 cycles
Primers annealing	30 sec	62°C	
Extension	1 min	68°C	
Final extension	5 min	68°C	
Hold	∞	12°C	

MAOA uVNTR is characterized by five possible alleles, leading to the separation of the following amplicons (**Figure 3.6**):

Amplicons (R= repeats)	Length
2R	294 bp
3R	324 bp
3.5R	342 bp
4R	354 bp
5R	384 bp

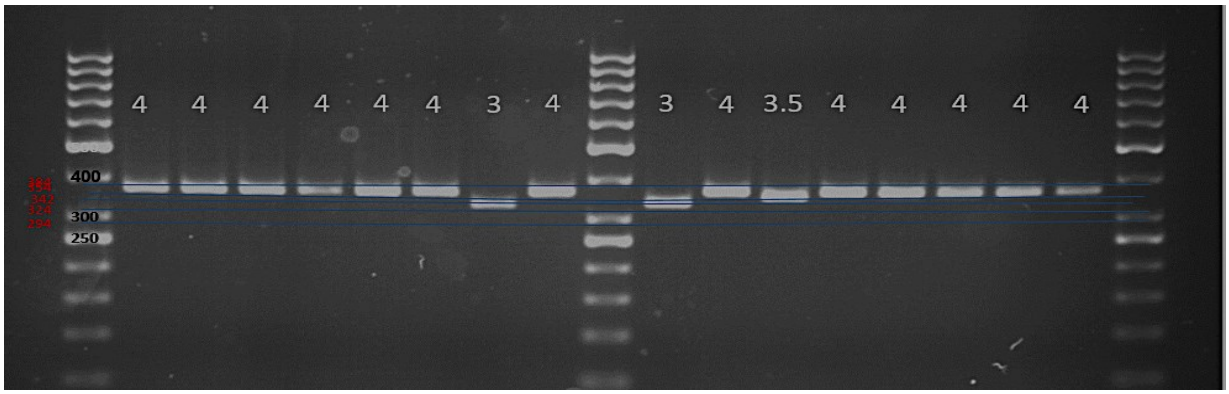

Figure 3.6. *MAOA* uVNTR amplicons visualized on a 2% agarose gel.

- ***SLC6A4* VNTR**

Reaction mix:

Reagent	Final concentration
Master mix 2x	1x
Primer forward: CGTTGCCGCTCTGAATGC	0.2 µM
Primer reverse: GGGAGATCCTGGGAGAGGT	0.2 µM
DNA	2.5 ng/µl
H_2O	Up to 20µl volume

PCR protocol:

DNA polymerase activation	4 min	94°C	
DNA denaturation	30 sec	94°C	35 cycles
Primers annealing	30 sec	60°C	
Extension	1 min	68°C	
Final extension	5 min	68°C	
Hold	∞	12°C	

The *SLC6A4* VNTR polymorphism is characterized by two possible alleles, leading to the separation of the following amplicons (**Figure 3.7**):

Amplicons	Length
Long (L, 16 repeats)	263 bp
Short (S, 14 repeats)	220 bp

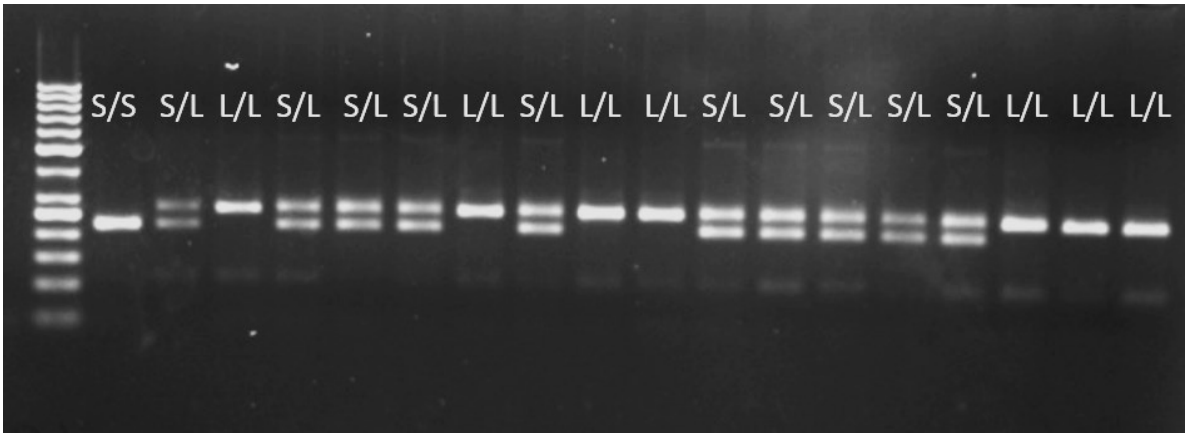

Figure 3.7. *SLC6A4* VNTR polymorphism amplicons visualized on a 2% agarose gel.

3.6.2. PCR-Restriction Fragment Length Polymorphism (PCR-RFLP)

DNA fragments containing the polymorphisms were amplifiedby PCR using the master mix described in chapter 3.5.2.

PCR products were subjected to enzymatic digestion. Digestion products were separated by electrophoresis on a 2% agarose gel, stained with ethidium bromide, together with a reference ladder with a resolution of 50 bp (GeneRuler DNA ladder, Thermo-Fisher Scientific).

- ***SLC6A4* rs25531 (A/G)**

SLC6A4 VNTR PCR products containing the Long allele were digested by the restriction enzyme MspI (New England BioLabs Inc.).

Reaction mix:

Reagent	Final concentration
Buffer Tango 10X	1x
MspI digestion enzyme	10U/µl
PCR product	1µg DNA
H_2O	Up to 31 µl

Digestion protocol:

Enzymatic digestion	3 h	37°C
Enzymatic inactivation	20 min	80°C
Hold	∞	12°C

In the presence of the G allele, the restriction enzyme MspI recognizes the sequence 5'-C|CGG-3', cutting the amplicon in two fragments of 97 bp and 166 bp, respectively (**Figure 3.8**). In the presence of the A allele, the enzymatic digestion does not take place and the amplicon length remains unchanged (263 bp) (**Figure 3.8**).

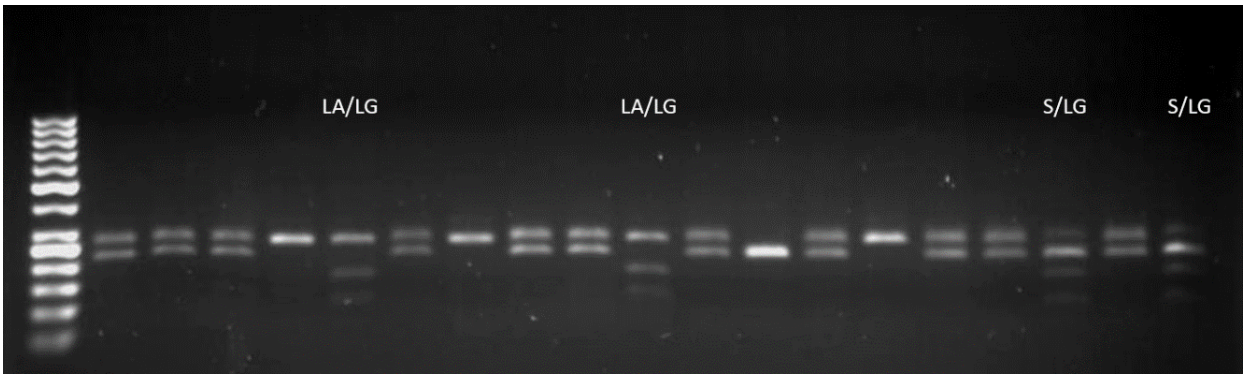

Figure 3.8. *SLC6A4* rs25531 digestion products visualized on a 2% agarose gel.

- ***DRD*4 rs1800955**

A DNA fragment of 190 bp containing the *DRD*4 rs1800955 was amplified.

Reaction mix:

Reagent	**Final concentration**
Master mix 2X	1X
Primer forward: GGATGAGCTAGGCGTCGG	0.07 µM
Primer reverse: CTCACCCTAGTCCACCTGG	0.07 µM
DNA	0.5 ng/µl
H_2O	Up to 25µl

PCR protocol:

DNA polymerase activation	4 min	94°C	
DNA denaturation	30 sec	94°C	35 cycles
Primers annealing	1.5 min	60°C	
Extension	1 min	68°C	
Final extension	5 min	68°C	
Hold	∞	12°C	

PCR products were digested by the restriction enzyme FspI (New England BioLabs Inc.):

Reagent	**Final concentration**
Buffer Tango 10X	1x
FspI digestion enzyme	0.2 U/µl
PCR product	1µg DNA
H2O	Up to 15 µl

Digestion protocol:

Enzymatic digestion	**15 min**	**37°C**
Enzyme inactivation/Hold	∞	**12°C**

In the presence of the T allele, the restriction enzyme FspI recognizes the sequence 5'-TGC|GCA-3', cutting the amplicon in two fragments of 70 bp and 120 bp, respectively (**Figure 3.9**). In the presence of the T allele, the enzymatic digestion does not take place and the amplicon length remains unchanged (190 bp) (**Figure 3.9**).

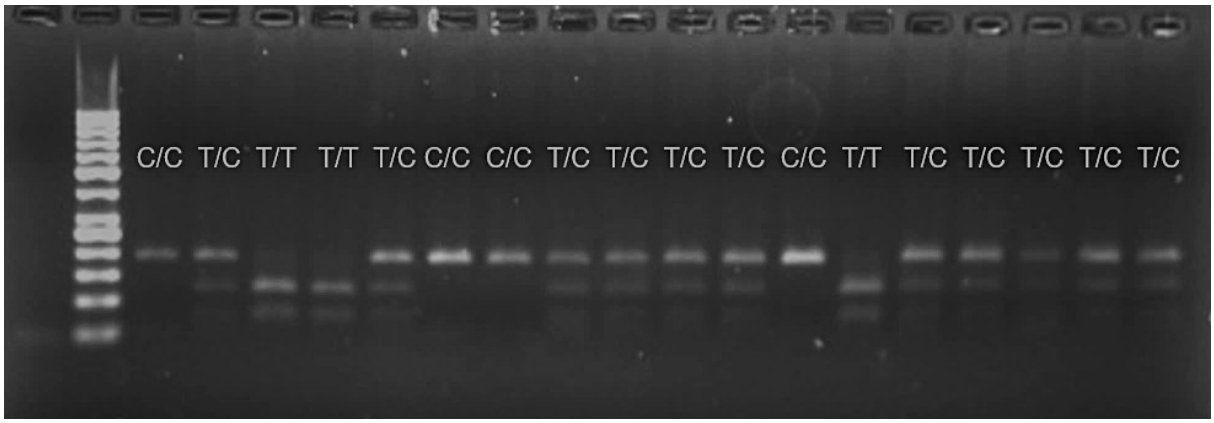

Figure 3.9. *DRD4* rs1800955 digestion products visualized on a 2% agarose gel.

3.6.3. PCR-High Resolution Melting (PCR-HRM)

DNA fragments containing the polymorphisms were amplified by PCR using the Type-it HRM PCR kit (Qiagen, Hilden, Germany):

Reagent	**Final concentration**
Master Mix type-it 2X	1X
Primer forward	700 nM
Primer reverse	700 nM
DNA	2.5 ng/µl
H_2O	Up to 10 µl

PCR was performed by using the CFX Connect Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA) by setting the following protocol:

Activation of HotStarTaq Plus DNA polymerase	**5 min**	**95°C**	
DNA denaturation	**10 sec**	**95°C**	45 cycles
Primers annealing	**30 sec**	**60°C**	
Extension	**10 sec**	**72°C**	
Denaturation	**1 min**	**95°C**	

At the end of the PCR amplification, the protocol comprised a DNA denaturation phase at 95°C for 60 seconds, a renaturation phase at 72°C for 90 seconds, and a progressive increment of temperature (0.2°C / 10 sec) to study the kinetics of denaturation of the amplicons.

- ***ANKK1* rs1800497**

A DNA fragment of 72 bp containing the *ANKK1* rs1800497 was amplified using the following primers:

- Primer forward: TGCAGCTCACTCCATCCTG
- Primer reverse: TTTGAGGATGGCTGTGTTGC

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 80°C to 90°C (**Figure 3.10**).

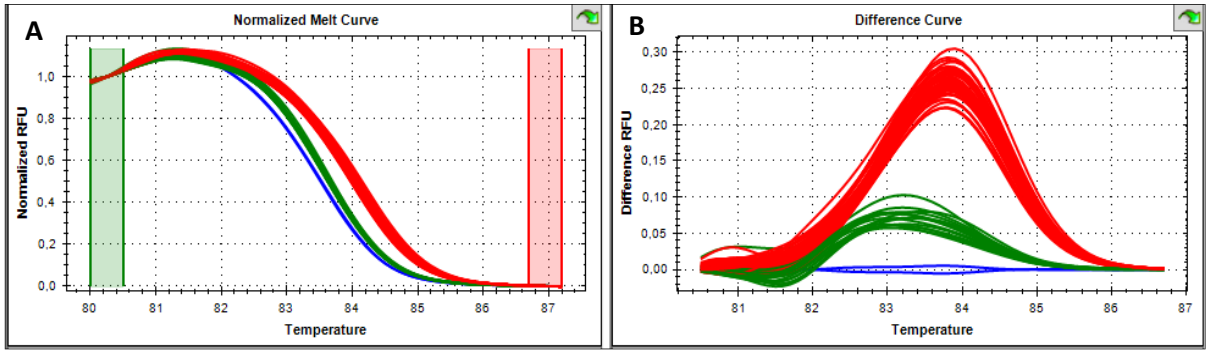

Figure 3.10. HRM analysis of the amplicons containing *ANKK1* rs1800497.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (C/C), in green the heterozygotes (A/T), in blue the homozygotes for minor allele (T/T). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***TH* rs6356**

A DNA fragment of 99 bp containing the *TH* rs6356 was amplified using the following primers:

- Primer forward: CTTTGAGGAGAAGGAGGGGA
- Primer reverse: ACCTCAAACACCTTCACAGC

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 80°C to 90°C (**Figure 3.11**).

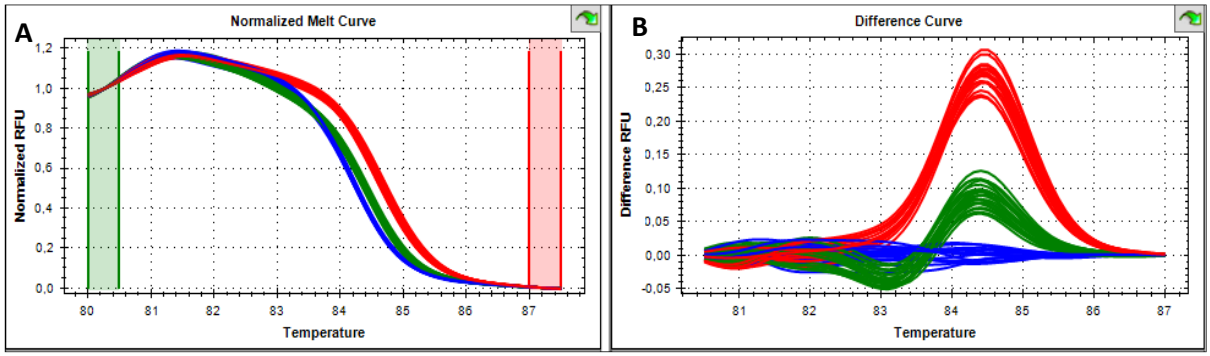

Figure 3.11. HRM analysis of the amplicons containing *TH* rs6356.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (G/G), in green the heterozygotes (A/G), in blue the homozygotes for minor allele (A/A). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***COMT* rs4680**

A DNA fragment of 69 bp containing the *COMT* rs4680 was amplified using the following primers:

- Primer forward: CAGCGGATGGTGGATTTC
- Primer reverse: TTCCAGGTCTGACAACGG

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 80°C to 90°C (**Figure 3.12**).

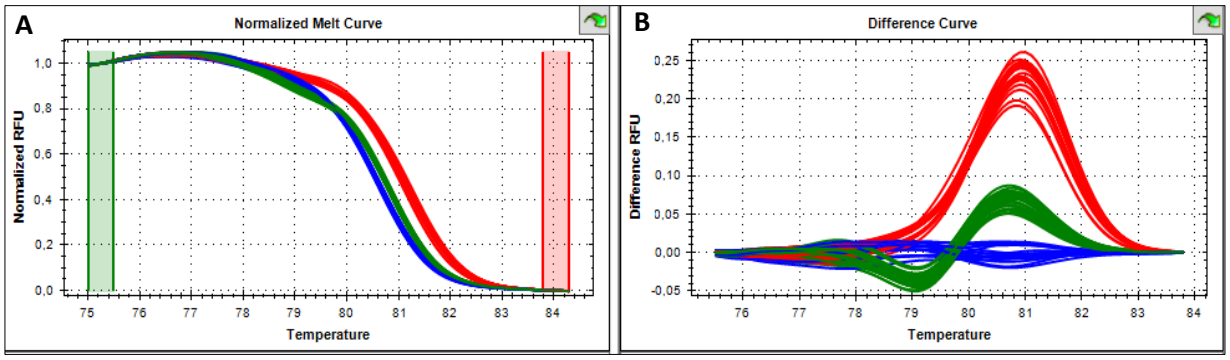

Figure 3.12 HRM analysis of the amplicons containing *COMT* rs4680.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (G/G), in green the heterozygotes (A/G), in blue the homozygotes for minor allele (A/A). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***OXTR* rs53576**

A DNA fragment of 88 bp containing the *OXTR* rs53576 was amplified using the following primers:

- Primer forward: AGCATTCATGGAAAGGAAAGG
- Primer reverse: GTAGAATGAGCTTCCCAG

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 77°C to 86°C (**Figure 3.13**).

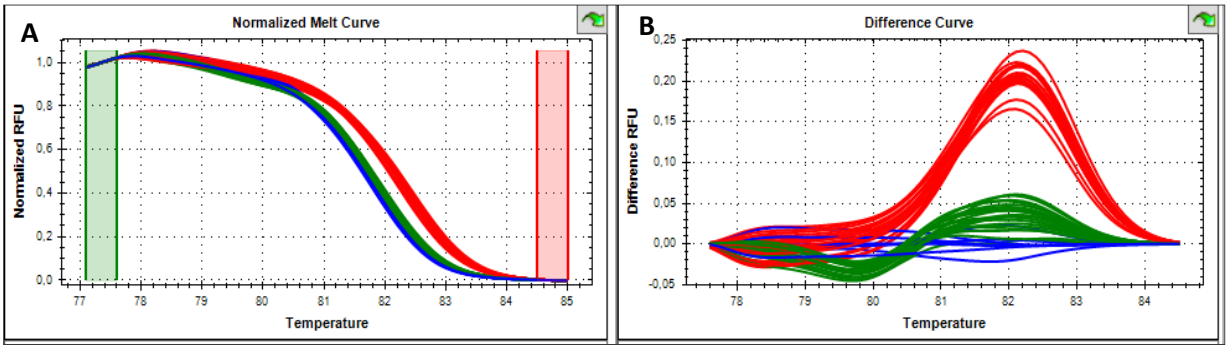

Figure 3.13. HRM analysis of the amplicons containing *OXTR* rs53576.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (G/G), in green the heterozygotes (A/G), in blue the homozygotes for minor allele (A/A). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***OXTR* rs1042778**

A DNA fragment of 89 bp containing the *OXTR* rs1042778 was amplified using the following primers:

- Primer forward: GAGTCCCCTATCATCTTC
- Primer reverse: GGTACCTATCAGTTTGTATC

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 75°C to 85°C (**Figure 3.14**).

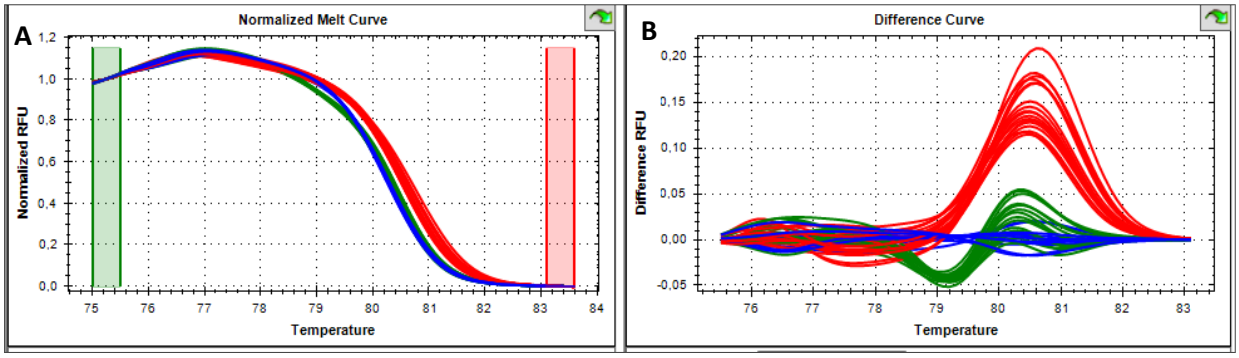

Figure 3.14. HRM analysis of the amplicons containing *OXTR* rs1042778.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (G/G), in green the heterozygotes (G/T), in blue the homozygotes for minor allele (T/T). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***OXTR* rs237885**

A DNA fragment of 70 bp containing the *OXTR* rs237885 was amplified using the following primers:

- Primer forward: AATGAGAAACACCACGATGCA
- Primer reverse: CTCTCAGAGTGGCACCCC

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 74°C to 85°C (**Figure 3.15**).

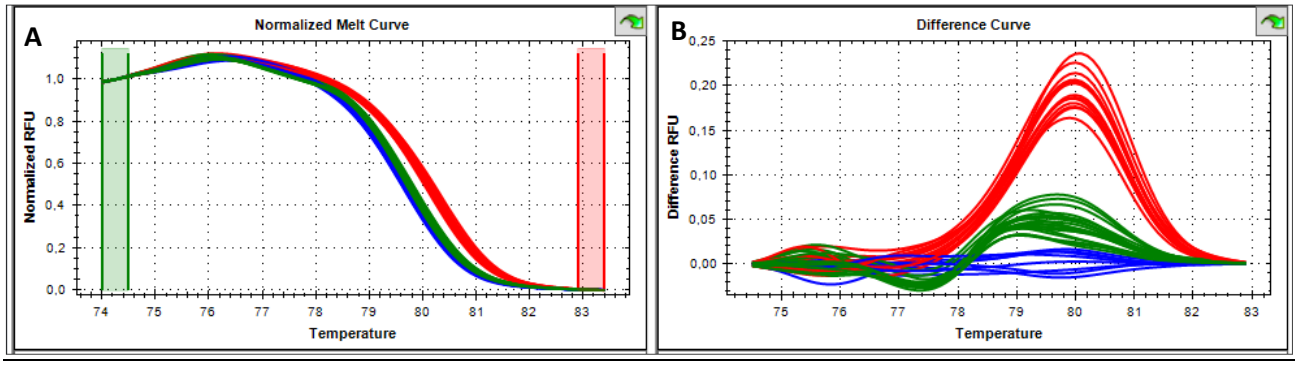

Figure 3.15. HRM analysis of the amplicons containing *OXTR* rs237885.
A) Normalized melt curve of the amplicons. In red the homozygotes for the minor allele (G/G), in green the heterozygotes (G/T), in blue the homozygotes for major allele (T/T). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***TPH2* rs4570625**

A DNA fragment of 165 bp containing the *TPH2* rs4570625 was amplified using the following primers:

- Primer forward: GCATCACAGGATTAAGAAGAAGC
- Primer reverse: TCTTATCCCTCCCATCAGCA

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 65°C to 85°C (**Figure 3.16**).

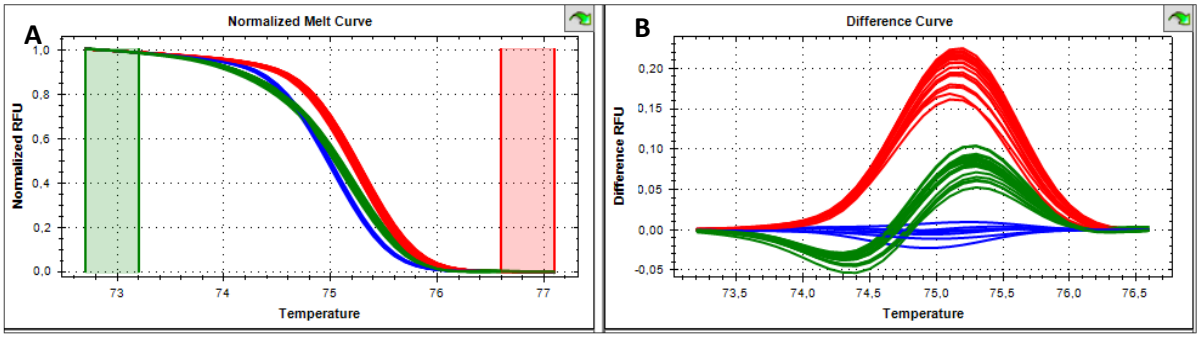

Figure 3.16. HRM analysis of the amplicons containing *TPH2* rs4570625.
Normalized melt curve of the amplicons. In blue the homozygotes for the minor allele (T/T), in green the heterozygotes (G/T), in red the homozygotes for major allele (G/G). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***5-HTR2A* rs6314**

A DNA fragment of 99 bp containing the *5-HTR2A* rs6314 was amplified using the following primers:

  - Primer forward: CAGGCTCTACAGTAATGACT
  - Primer reverse: TCACAGGAAAGGTTGGTT

To study the kinetics of denaturation of DNA, the temperature was progressively raised from70°C to 80°C (**Figure 3.17**).

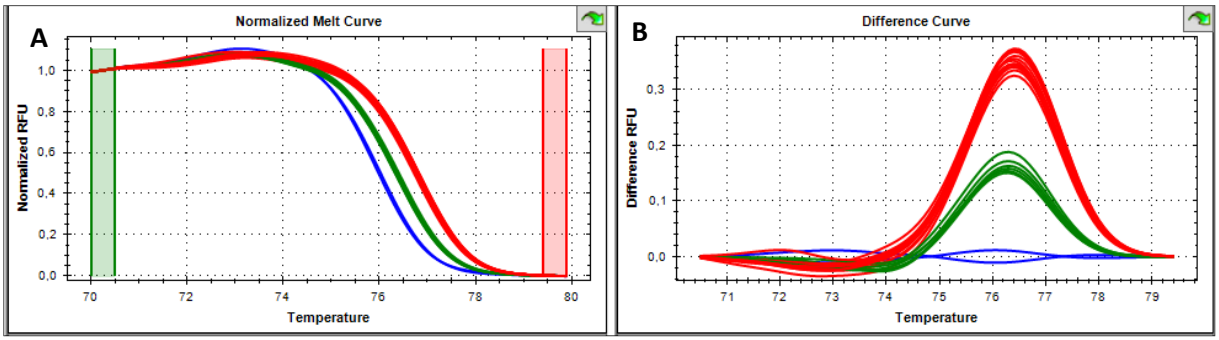

Figure 3.17. HRM analysis of the amplicons containing *5-HTR2A* rs6314.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (C/C), in green the heterozygotes (C/T), in blue the homozygotes for minor allele (T/T). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference.

- ***5-HTR1B* rs13212041**

A DNA fragment of 81 bp containing the *5-HTR1B* rs13212041 was amplified using the following primers:

  - Primer forward: AGTGACAGGTACATGAAATTAAGAGA
  - Primer reverse: AACAAACAAACCATTATGTGTGCTA

For this SNP, we used a different protocol for the PCR:

Activation of HotStarTaq Plus DNA polymerase	**5 min 95°C**	
DNA denaturation	**10 sec 95°C**	40 cycles
Primers annealing	**30 sec 60°C**	
Denaturation	**1 min 95°C**	
Renaturation	**1.5 min 72°C**	

To study the kinetics of denaturation of DNA, the temperature was progressively raised from 70°C to 85°C (**Figure 3.18**).

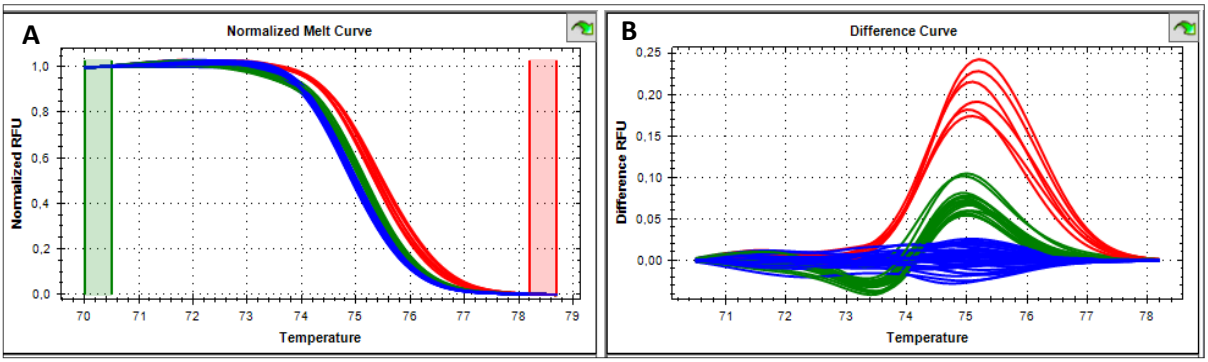

Figure 3.18. HRM analysis of the amplicons containing *5-HTR1B* rs13212041.
A) Normalized melt curve of the amplicons. In red the homozygotes for the major allele (T/T), in green the heterozygotes (C/T), in blue the homozygotes for minor allele (C/C). **B)** Difference plot: curve differences were magnified by subtracting each curve from a user-defined genotype reference

3.7. Statistical analysis

The statistical analysis was performed by the SPSS *Advanced Statistics* v21 (IBM Corporation, Armonk, NY, USA) softwarepackage.

- **Preliminary analyses**
  a) Data distribution: Shapiro-Wilk normality test was used to assess the deviation form a normal distribution of each psychometric, environmental, anddemographic variable.
  b) Search for confounding factors: for each psychometric variable, the identification of confounding factors, such as age and IQ, was performed by the Spearman's rank-order correlation analysis. The Mann–Whitney U test was used to evaluate the influence of ethnicity (Latin/Hispanic and not-Latin/Hispanic) on PCL-R and PCL:YV scores in incarcerated adults and adolescents, respectively, and to investigate the influence of ADHD symptoms on APSD scores in youths with CD.
  c) Collinearity: we performed Spearman's rank-order correlations between psychopathic scores, as well as between demographic variables. Correlation coefficients equal or higher than 0.9 indicated collinearity between variables.
  d) Hardy-Weinberg equilibrium (H-Weq): for each polymorphism, the respect/departure from the H-W eq was evaluated by a Chi-Square (χ^2) test.
  e) Fisher's Exact Test: for each polymorphism, we compared genotype groupings of Latin/Hispanics with not-Latin/Hispanics in the sample of incarcerated adults and incarcerated adolescents.
  f) Allele frequencies: for each polymorphism, we compared the allele frequencies observed in each sample with those of European-ancestry populations as reported by the 1000Genome project for SNPs, or by the scientific literature for 5-HTTLPR, *MAOA* uVNTR, *DRD4* exonIII VNTR and DAT1 3'UTR VNTR. (Doucette-Stamm et al., 1995; Chang et al., 1996; Sabol et al., 1998; Haberstick et al., 2015).
- **Associations between environmental factors and psychopathy scores**
  The correlations between PCL-R (Total, Factor 1, and Factor 2) scores and MOPS (Maternal and Paternal) scores and between APSD (Total and CU) scores and MI (Total and Active maltreatment) scores were investigated by the Generalized Estimating Equations (GEEs) with an exchangeable working matrix. To identify which distribution was the best fitting for GEE, Goodness of fit was computed using the Quasi-Likelihood under independence model criterion (QIC). Based on the small-is-better criteria, QIC values indicated that the Tweedie

distribution model with identity link function was better than the Linear distribution model with identity link function.

GEEs were developed by Liang and Zeger (1986) to obtain more efficient and unbiased regression estimates for not-normal variables and can be used for, but not exclusively to, longitudinal or repeated measure analyses. Moreover, according to Fumagalli and colleagues (2010), GEEs provide a valid framework to analyze correlated data that show different distributions (Hardin & Hilbe, 2013).

The linear regression analysis was used to evaluate the percentage of psychopathy (PCL-R scores or APSD scores) variance explained by environmental factors (MOPS scores or MI scores) in incarcerated adults and in youths with CD.

- **Genetic association analysis**

For each polymorphism, two genotype groupings were created by grouping together the heterozygotes with the homozygotes for the less frequent allele:

- *5-HTR1B* rs13212041: T/T versus C allele (C/T + C/C)
- *5-HTR2A* rs6314: C/C versus T allele (C/T + T/T)
- *TPH2* rs4570625: G/G versus T allele (G/T + T/T)
- 5-HTTLPR (VNTR + rs23551): L/L (L_A/L_A+ L_A/XL) versus S allele (S/L_A+ L_G/L_A + S/S + S/L_G)
- *MAOA* uVNTR: Low (2R + 3R + 5R) versus High (4R + 3.5R)
- *COMT* rs4680: G/G versus A allele (A/G + A/A)
- *DRD4* exonIII VNTR: 4/4 versus not-4/4 (2/4 + 3/4 + 4/10 + 4/11 + 4/5 +4/6 +4/7 + 4/8 + 2/2 + 2/3 +2/5 + 2/6 + 2/7 + 2/8 + 3/3 + 3/5 + 3/7 + 3/9 + 5/7 + 5/10 + 6/7 + 7/7 + 7/8 + 8/10)
- *DRD4* rs1800955: T/T versus C allele (T/C + C/C)
- *SLC6A3* 3'UTR VNTR: 9R (9/3 + 9/6 + 9/7 + 9/9 + 9/10 + 9/11) versus not-9R (10/3 + 10/7 + 10/8 + 10/10 + 10/11)
- *ANKK1* rs1800497: C/C versus T allele (C/T + T/T)
- *TH* rs6356: G/G versus A allele (G/A + A/A)
- *OXTR* rs53576: G/G versus A allele (G/A + A/A)
- *OXTR* rs1042778: G/G versus T allele (G/T + T/T)
- *OXTR* rs2378865: G/G versus T allele (G/T + T/T)

This strategy allowed us to increase the power of the statistical analysis by substantially reducing the degrees of freedom.

The association analyses between each genotype grouping and PCL-R (Total, Factor 1 and Factor 2) scores, or PCL:YV (Total, Factor 1 and Factor 2) scores, or APSD (Total and CU) scores were investigated by the GEEs.
The linear regression analysis was used to evaluate the percentage of psychopathy (PCL-R scores, or PCL:YV scores, or APSD scores) variance explained by genetic factors.

We investigated whether the genetic variants found directly associated with PCL-R or APSD scores represent significant moderators of the relationships between MOPS scores and PCL-R scores, or between MI scores and APSD scores. We assessed the violation of homoskedasticity assumption by the Koenker test using the heteroskedasticityv3 macro for SPSS implemented by Ahmad Daryanto. Then, we performed a simple moderation analysis using Process_v4.2._beta macro for SPSS, which was implemented by Andrew F. Hayes http://www.afhayes.com/. Cribari-Neto correction was applied to control for deviations from the normal distribution.

Moreover, the GEEs and linear regression were used to evaluate the interactive effect between genotype groupings and environmental factors (MOPS scores or MI scores) on psychopathy (PCL-R scores or APSD scores).
Finally, the genetic variants that emerged significantly associated with psychopathy were analyzed in interaction two by two and three by three.

An a priori power analysis for two-group independent sample t-test was conducted by using G*power 3.1.9.2 software (University of Düsseldorf) to predict the required sample size necessary to replicate the significant findings observed in the sample of incarcerated adults and in the sample of incarcerated adolescents (Cohen's coefficient, "d") by setting a minumun power of 0.85 (Cohen, 1988), while a post hoc power analysis was conducted to determine the power (1-β) of the analyses and the effect sizes (Cohen's coefficient, "d") of the observed differences between means.

Due to its low sample size, the group of incarcerated adolescents was used to investigate only the significant findings obtained in the larger sample of incarcerated adults.

For the same reason, also the group of youths with CD was used to investigate only the significant associations observed in the sample of incarcerated adults.

Each p_{value} obtained from the statistical analyses was corrected according to the Bonferroni method (p_{Bonf}), in order to limit the type I error (false positive results).

To satisfy the Bonferroni correction method, each p_{value} was corrected by considering the number of simultaneously performed statistical tests taking into account two PCL-R subscales, two MOPS subscales, fourteen genetic variants and two PCL:YV subscales.

Chapter 4

Results

4.4. US incarcerated participants

4.1.1 Incarcerated adults

4.1.1.1. Distribution of psychometric, environmental, and demographic variables

Shapiro-Wilk normality test indicated that the distribution of the demographic (age and IQ), psychometric (PCL-R), and environmental (MOPS) variables significantly deviated from the Gaussian distribution (**Table 4.1**).

Variables	Mean ± SD	Statistics	df	p_{value}
Age	34.95±9.65	0.966	919	**$< 10^{-6}$**
IQ	98.45±13.40	0.991	916	**$< 10^{-6}$**
PCL-R Total	20.70±6.70	0.995	919	**6×10^{-3}**
PCL-R Factor 1	6.12±3.41	0.976	919	**$< 10^{-6}$**
PCL-R Factor 2	12.36±3.96	0.967	919	**$< 10^{-6}$**
Paternal MOPS	11.90±10.97	0.883	220	**$< 10^{-6}$**
Maternal MOPS	8.50±7.78	0.820	247	**$< 10^{-6}$**

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Table 4.1. Descriptive data and normality test for age, IQ, PCL-R Total, PCL-R Factor 1, PCL-R Factor 2, Paternal MOPS, and Maternal MOPS variables in the sample of incarcerated adults. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style, SD= standard deviation, df= degrees of freedom.

Mean Maternal MOPS scores (8.50±7.78) were significantly lower than mean Paternal MOPS scores (11.90±10.97) (Wilcoxon signed-rank test: $Z= 4.466$, $p< 10^{-4}$).

Ninety-three (11.7%) of incarcerated adults scored 30 or higher at the PCL-R questionnaire.

4.1.1.2. Search for collinearity between variables and confounding factors

The Spearman's rank-order correlation test indicated no significant collinearity between variables (**Table 4.2**).

The Spearman's rank-order correlation test indicated that age and IQ significantly influence PCL-R Total, Interpersonal/Affective and Lifestyle/Antisocial scores. The Mann–Whitney U test indicated ethnicity as confounding factor for PCL-R scores (**Table 4.2**) as Latin/Hispanics showed lower PCL-R Interpersonal/Affective scores (5.355±2.946) but

higher PCL-R Lifestyle/Antisocial scores (12.981±2.946) compared to not-Latin/Hispanics (PCL-R Interpersonal/Affective scores: 6.710±3.622; PCL-R Lifestyle/Antisocial scores: 11.872±4.179).

	Age	**IQ**	**Ethnicity**	**PCL-R Total**	**PCL-R Factor 1**	**PCL-R Factor 2**
Age		ρ_s= 0.050 df= 916 p_{value}= 0.117	ρ_s= 0.157 df= 916 p_{value}= **10^{-6}**	ρ_s= -0.147 df= 919 p_{value}< **10^{-6}**	ρ_s= -0.069 df= 919 p_{value}= 3.7×**10^{-2}**	ρ_s= -0.205 df= 919 p_{value}< **10^{-6}**
IQ	ρ_s= 0.050 df= 916 p_{value}= 0.117		ρ_s= 0.274 df= 916 p_{value}< **10^{-6}**	ρ_s= 0.018 df= 916 p_{value}= 0.583	ρ_s= 0.055 df= 916 p_{value}= 0.094	ρ_s= -0.027 df= 916 p_{value}= 0.415
Ethnicity	ρ_s= 0.157 df= 916 p_{value}= **10^{-6}**	ρ_s= 0.274 df= 916 p_{value}< **10^{-6}**		Z= 0.353 p_{value}= 0.724	Z= 4.497 p_{value}< **10^{-6}**	Z= -4.148 p_{value}< **10^{-6}**
PCL-R Total	ρ_s= -0.147 df= 919 p_{value}< **10^{-6}**	ρ_s= 0.018 df= 916 p_{value}= 0.583	Z= 0.353 p_{value}= 0.724			
PCL-R Factor 1	ρ_s= -0.069 df= 919 p_{value}= 3.7×**10^{-2}**	ρ_s= 0.055 df= 916 p_{value}= 0.094	Z= 4.497 p_{value}< **10^{-6}**			ρ_s= 0.406 df= 916 p_{value}< **10^{-6}**
PCL-R Factor 2	ρ_s= -0.205 df= 919 p_{value}< **10^{-6}**	ρ_s= -0.027 df= 916 p_{value}= 0.415	Z= -4.148 p_{value}< **10^{-6}**		ρ_s= 0.406 df= 916 p_{value}< **10^{-6}**	

Table 4.2. **Search for collinearity between variables and confounding factors in the sample of incarcerated adults.** Spearman's rank-order correlations (ρ_s) between PCL-R Factor 1 and PCL-R Factor 2 scores, and between age, IQ and ethnicity. Spearman's rank-order correlations between PCL-R scores and age and between PCL-R scores and IQ; Mann–Whitney U test (Z) to compare PCL-R scores of Latin/Hispanics with those of not-Latin/Hispanics. PCL-R= Psychopathy Checklist-Revised, IQ= Intelligence Quotient, df= degrees of freedom. PCL-R Factor 1= Interpersonal/Affective, PCL-R Factor 2= Lifestyle/Antisocial

4.1.1.3 Hardy-Weinberg equilibrium, Fisher's Exact Test and allele frequencies

The Chi-Square test showed that the allele and genotype frequencies were in Hardy-Weinberg equilibrium, except for the *TPH2* rs4570625 (χ^2= 4.66, p= 0.031).

In the whole sample, the frequencies of *TPH2* rs4570625 (p= 10^{-4}), 5-HTTLPR (p= 2.1×10^{-2}), *TH* rs6356 (p= 2×10^{-3}), *ANKK1* rs1800497 (p= 10^{-4}), and *COMT* rs4680 (p= 3×10^{-3}) genotypes gounpings were significantly different between Latin/Hispanics and not Latin/Hispanics (**Table 4.3**). Concerning the subsample of incarcerated adults with MOPS data, the frequencies of *TH* rs6356 (p= 1.2×10^{-2}), *ANKK1* rs1800497 (p= 3×10^{-2}) DRD4

exonIII VNTR (p= 1.2×10^{-2}), and *COMT* rs4680 (p= 1.3×10^{-2}) genotypes gounpings were significantly different between Latin/Hispanics and not Latin/Hispanics (**Table 4.3**).

Pathways	Genetic variants	Whole sample				Whole sample divided by ethnicity			Subjecs with MOPS data divided by ethnicity		
		Genotype groupings	Genotypes	N	H-W eq	L/H	Not L/H	Fisher's Exact Test	L/H M	Not L/H M	Fisher's Exact Test
Dopaminergic	*COMT* rs4680	A allele	A/A	208	χ^2= 0.001 p= 0.973	66	142	**p= 0.003**	19	23	**p= 0.013**
			A/G	482		220	262		52	51	
		G/G	G/G	278		148	130		48	23	
	DRD4 exonIII VNTR	4/4	4/4	394	χ^2= 1.134 p= 0.287	167	227	p= 0.099	38	47	**p= 0.012**
		not-4/4	2/4	85		33	52		8	11	
			3/4	38		8	30		4	2	
			4/10	2		2	0		0	0	
			4/11	1		0	1		0	0	
			4/5	33		25	8		8	3	
			4/6	25		20	5		5	3	
			4/7	261		133	128		44	15	
			4/8	13		4	9		1	1	
			2/2	6		1	5		0	0	
			2/3	5		0	5		0	0	
			2/5	1		0	1		0	0	
			2/6	2		2	0		1	0	
			2/7	32		11	21		4	8	
			2/8	1		0	1		0	0	
			3/3	3		2	1		2	0	
			3/5	2		0	2		0	1	
			3/7	6		2	4		0	1	
			3/9	1		0	1		0	0	
			5/10	1		1	0		0	0	
			5/7	3		2	1		0	1	
			6/7	5		4	1		1	0	
			7/7	53		25	28		5	2	
			7/8	4		0	1		0	1	
			8/10	1		1	0		0	0	
	DRD4 rs1800955	C allele	C/C	197	χ^2= 3.50 p= 0.061	75	122	p= 0.412	19	24	p= 1
			T/C	450		209	241		59	28	
		T/T	T/T	328		156	172		42	34	
	SLC3A6 3'UTR VNTR	9R	9/11	3	χ^2= 0.002 p= 0.967	1	2	p= 0.095	0	0	p= 0.072
			9/10	344		143	201		36	42	
			9/9	53		21	32		8	5	
			9/3	2		2	0		0	0	
		not-9R	10/11	15		5	10		1	3	
			10/10	554		268	286		76	46	
			10/8	3		1	2		1	0	
			10/7	3		1	2		0	0	
			10/3	2		2	0		0	0	
	ANKK1 rs1800497	T allele	T/T	73	χ^2= 0.212 p= 0.645	55	18	**p= 0.0001**	18	1	**p= 0.03**
			C/T	400		223	177		57	43	
		C/C	C/C	509		166	343		48	53	
	TH rs6356	A allele	A/A	176	χ^2= 1.288 p= 0.256	92	84	**p= 0.002**	26	14	**p= 0.012**
			G/A	456		217	239		67	44	

		G/G	G/G	343		121	212		29	39	
Oxytocinergic	*OXTR* rs53576	A allele	A/A	110	χ^2= 1.40 p= 0.237	65	45	p= 0.101	15	7	p= 0.783
			G/A	457		207	250		55	46	
		G/G	G/G	401		166	235		51	42	
	OXTR rs1042778	T allele	T/T	171	χ^2= 1.566 p= 0.211	82	89	p= 1	27	19	p= 0.304
			G/T	451		182	259		60	43	
		G/G	G/G	351		165	186		34	33	
	OXTR rs237885	T allele	T/T	191	χ^2= 0.03 p= 0.861	90	101	p= 0.167	27	23	p= 0.769
			T/G	485		211	274		55	44	
		G/G	G/G	301		141	160		40	29	
Serotonergic	*5-HTR1B* rs13212041	C allele	C/C	42	χ^2= 2.123 p= 0.145	20	22	p= 0.239	5	6	p= 0.3
			T/C	287		117	170		28	26	
		T/T	T/T	654		308	346		89	64	
	MAOA uVNTR	High	4R	632	Not applicable	281	351	p= 1	77	60	p= 0.888
			3.5R	15		6	9		1	1	
		Low	5R	7		1	6		1	2	
			3R	326		156	170		44	34	
			2R	3		2	1		0	0	
	5-HTTLPR	L/L	L_A/ L_A+ L_A /XL	218	χ^2= 0.059 p= 0.81	81	137	**p= 0.021**	22	24	p= 0.244
		S allele	S/ L_A+ L_G/ L_A	484		222	262		63	49	
			S/S + S/ L_G	282		143	139		38	24	
	TPH2 rs4570625	T allele	T/T	80	**χ^2= 4.66 p= 0.031**	56	24	**p= 0.0001**	15	3	p= 0.168
			G/T	349		173	176		45	36	
		G/G	G/G	538		203	335		58	57	
	5-HTR2A rs6314	T allele	T/T	2	χ^2= 3.258 p= 0.071	1	1	p= 1	1	0	p= 0.6
			C/T	151		67	84		23	16	
		C/C	C/C	830		376	454		98	81	

Table 4.3. Genotype groupings, genotypes, sample size (N), and Chi-square (χ^2) test to evaluate the Hardy-Weinberg equilibrium. Latin/Hispanics and not-Latin/Hispanics were analyzed by the exact Fisher's test in whole sample and the subsample with MOPS data: Latin/Hispanic and not-Latin/Hispanic, and the exact Fisher's test. MOPS= Measure of Parental Style; L/H= Latin/Hispanics, not-L/H= not Latin/Hispanics, H-W eq= Hardy-Weinberg equilibrium.

The comparison of the allele frequencies observed in the sample of incarcerated adults with those reported by 1000Genomes for the Europen-ancestry population showed remarkable differences in the frequencies of *ANKK1* rs1800497 T allele, and *TPH2* rs4570625 T allele observed in Latin-Hispanics (**Table 4.4**). Specifically, Latin/Hispanics exceded the allele frequencies reported by 1000 Genomes by 19%, and 11%, respectively.

Polymorphisms	**Allelic variants**	**Incarcerated adults (whole sample)**			**Incarcerated adults (subsample with MOPS data)**			**European ancestry**
		Total	**L/H**	**not-L/H**	**Total**	**L/H**	**not-L/H**	
COMT rs4680	G allele	0.54	0.59	0.49	0.58	0.62	0.50	0.51
	A allele	0.46	0.41	0.51	0.42	0.38	0.50	0.49
DRD4 exonIII VNTR	4R allele	0.64	0.63	0.65	0.63	0.60	0.67	0.64*
	7R allele	0.21	0.23	0.20	0.21	0.24	0.16	0.21*
DRD4 rs1800955	C allele	0.43	0.40	0.45	0.42	0.40	0.44	0.44
	T allele	0.57	0.60	0.55	0.57	0.60	0.56	0.56
DAT1 3'UTR VNTR	9R allele	0.23	0.21	0.25	0.24	0.21	0.27	0.27*
	10R allele	0.75	0.77	0.74	0.75	0.78	0.71	0.72*
ANKK1	C allele	0.72	0.63	0.80	0.69	0.62	0.77	0.82

rs1800497	T allele	0.28	0.37	0.20	0.31	0.38	0.23	0.18
TH rs6356	G allele	0.59	0.53	0.62	0.56	0.51	0.63	0.60
	A allele	0.41	0.47	0.38	0.44	0.49	0.37	0.40
OXTR rs53576	G allele	0.65	0.62	0.68	0.66	0.65	0.68	0.66
	A allele	0.35	0.38	0.32	0.34	0.35	0.32	0.34
OXTR rs1042778	G allele	0.59	0.60	0.59	0.55	0.53	0.57	0.63
	T allele	0.41	0.40	0.41	0.45	0.47	0.43	0.37
OXTR rs237885	G allele	0.56	0.56	0.55	0.54	0.55	0.53	0.51
	T allele	0.44	0.44	0.45	0.46	0.45	0.47	0.49
5-HTR1B rs13212041	C allele	0.19	0.18	0.20	0.18	0.16	0.20	0.19
	T allele	0.81	0.82	0.80	0.82	0.84	0.80	0.81
TPH2 rs4570625	G allele	0.73	0.68	0.79	0.73	0.68	0.78	0.79
	T allele	0.27	0.32	0.21	0.27	0.32	0.22	0.21
5-HTR2A rs6314	C allele	0.92	0.92	0.92	0.91	0.90	0.92	0.92
	T allele	0.08	0.08	0.08	0.09	0.10	0.08	0.08
MAOA uVNTR	4R allele	0.64	0.63	0.65	0.62	0.63	0.62	0.65*
	3R allele	0.33	0.35	0.32	0.35	0.36	0.35	0.33*
5-HTTLPR	L allele	0.47	0.43	0.50	0.46	0.42	0.50	0.50*
	S allele	0.53	0.57	0.50	0.54	0.58	0.50	0.50*

Table 4.4. Allelic variants, allelic frequencies observed in incarcerated adults Latin/Hispanic and not-Latin/Hispanic in both full sample and the subgroup of subjects with MOPS data, compared with expected allelic frequencies in European-anchestral population. MOPS= Measure of Parental Style; L/H= Latin/Hispanics, not-L/H= not Latin/Hispanics. *Allele frequencies obtained from literature data.

4.1.1.4 Correlations between PCL-R scores and MOPS scores

Paternal MOPS scores significantly correlated with PCL-R Total (χ^2= 8.984, df= 1, $p_{value}= 3\times10^{-3}$, $p_{Bonf.}= 6\times10^{-3}$; **Figure 4.1a**), Interpersonal/Affective (χ^2= 6.570, df= 1, $p_{value}= 1.1\times10^{-2}$, $p_{Bonf.}= 2.2\times10^{-2}$; **Figure 4.1b**) and Lifestyle/Antisocial (χ^2= 6.276, df= 1, $p_{value}= 1.2\times10^{-2}$,$p_{Bonf.}= 2.4\times10^{-2}$; **Figure 4.1c**) scores, explaining 4.6% (R^2= 0.051, $F_{1,209}$= 11.115, $p_{value}= 1\times10^{-3}$, β= 0.225; $\beta_{Latin/Hispanics}$= 0.270, $p_{value} < 0.05$, N= 119; $\beta_{not\text{-}Latin/Hispanics}$= 0.166, $p_{value} > 0.05$, N= 91), 4.1% (R^2= 0.046, $F_{1,209}$= 11.115, $p_{value}= 1\times10^{-3}$, β= 0.214; $\beta_{Latin/Hispanics}$= 0.243, $p_{value} < 0.05$, N= 119; $\beta_{not\text{-}Latin/Hispanics}$= 0.148, $p_{value} > 0.05$, N= 91), and 1.7% (R^2= 0.022, $F_{1,209}$= 4.677, $p_{value}= 3.2\times10^{-2}$, β= 0.148; $\beta_{Latin/Hispanics}$= 0.194, $p_{value} < 0.05$, N=119; $\beta_{not\text{-}Latin/Hispanics}$= 0.116, $p_{value} > 0.05$, N= 91) of the variance, respectively.

Maternal MOPS scores were not significantly correlated to PCL-R Total scores (χ^2= 4.667, df= 1, p_{value}= 0.062, $p_{Bonf.}$= 0.124).

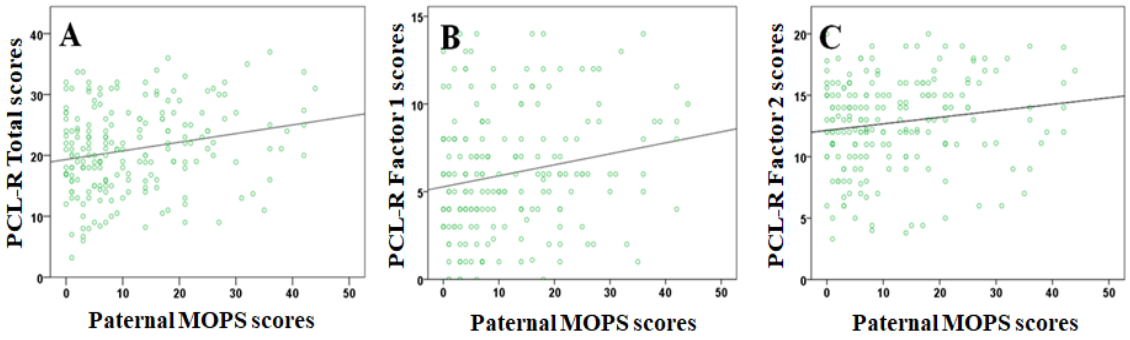

Figure 4.1. Correlations between Paternal MOPS scores and PCL-R scores in incarcerated adults. A) PCL-R Total, B) PCL-R Factor 1, and C) PCL-R Factor 2. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style. PCL-R Factor 1= Interpersonal/Affective, PCL-R Factor 2= Lifestyle/Antisocial

4.1.1.5 Associations between genetic variants and PCL-R scores

a) Serotonergic polymorphisms

Carriers of the *5-HTR1B* rs13212041 T/T genotype showed a mean PCL-R Total score (21.74±6.29) significantly higher than C allele carriers (20.16±6.22) (χ^2= 11.989, df= 1, p_{value}= 1×10^{-3}, $p_{Bonf.}$= 1.4×10^{-2}; 1-β= 0.95, d= 0.25; **Figure 4.2a**). Linear regression showed that *5-HTR1B* rs13212041 T/T genotype produced a significant model that explained 1.2% of the variance of PCL-R Total scores (R^2= 0.014, $F_{1,790}$= 10.862, p= 1×10^{-3}, β= 0.116; $\beta_{Latin/Hispanics}$= 0.140, p_{value} < 0.05, N= 353; $\beta_{not\text{-}Latin/Hispanics}$= 0.101, p_{value} < 0.05, N= 437).

Moreover, the *5-HTR1B* rs13212041 T/T carriers scored higher than C allele carriers at both PCL-R Interpersonal/Affective (T/T: 6.37±3.41, C allele= 5.74±3.11; χ^2= 8.934, df= 1, p_{value}= 3×10^{-3}, $p_{Bonf.}$= 6×10^{-3};1-β= 0.95, d= 0.19; **Figure 4.2b**) and Lifestyle/Antisocial (T/T: 13.09±3.85, C allele= 12.21±3.85; χ^2= 11.551, df= 1, p_{value}= 1×10^{-3}, $p_{Bonf.}$= 2×10^{-3}; 1-β= 0.99, d= 0.23; **Figure 4.2c**). Linear regression showed that *5-HTR1B* rs13212041 T/T genotype produced a significant model that explained 0.5% of the variance of PCL-R Interpersonal/Affective scores (R^2= 0.007, $F_{1,790}$= 5.185, p= 2.3×10^{-2}; β= 0.08; $\beta_{Latin/Hispanics}$= 0.142, p_{value} < 0.05, N= 353; $\beta_{not\text{-}Latin/Hispanics}$= 0.059, p_{value} > 0.05, N= 437) and 1.4% of the variance of PCL-R Lifestyle/Antisocial scores (R^2= 0.015, $F_{1,790}$= 12.034, p= 1×10^{-3}; β= 0.122; $\beta_{Latin/Hispanics}$= 0.117, p_{value} < 0.05, N= 353; $\beta_{not\text{-}Latin/Hispanics}$= 0.118, p_{value} < 0.05, N= 437).

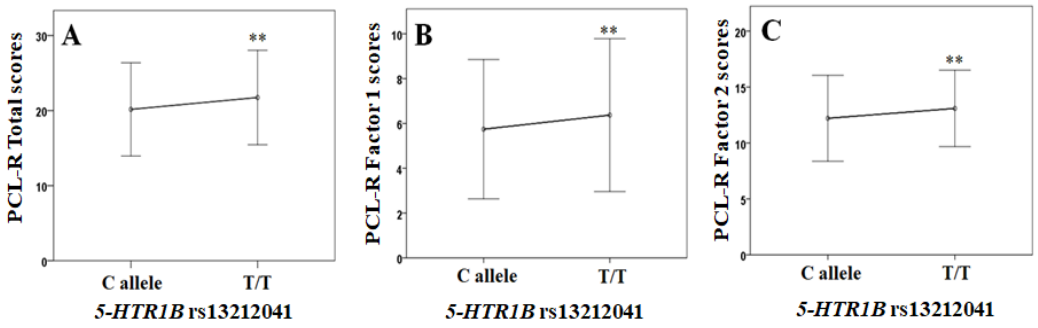

Figure 4.2. Associations between *5-HTR1B* rs13212041 and PCL-R scores in incarcerated adults. A) PCL-R Total, B) PCL-R Factor 1, and C) PCL-R Factor 2. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style. PCL-R Factor 1= Interpersonal/Affective, PCL-R Factor 2= Lifestyle/Antisocial

None of the other serotonergic polymorphisms showed any statistically significant association with PCL-R scores (**Table 4.5**).

Polymorphism	χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
5-HTR1B rs13212041	11.898	1	1×10^{-3}	**1.4×10^{-2}**
MAOA uVNTR	0.005	1	0.945	1
5-HTTLPR	0.060	1	0.807	1
5-HTR2A rs6314	0.942	1	0.332	1
TPH2 rs4570625	2.260	1	0.133	1

Table 4.5. Associations between the serotonergic polymorphisms and PCL-R Total scores in incarcerated adults. Alpha level= 0.05/14 genetic variants= 0.0036. df= degrees of freedom.

A priori power analyses suggested that in order to observe a significant difference in PCL-R Total scores, PCL-R Interpersonal/Affective scores, and PCL-R Lifestyle/Antisocial scores, between *5-HTR1B* rs13212041 T/T genotype carriers and *5-HTR1B* rs13212041 C allele carriers, 518, 896, and 612 are the minimum sample sizes required, respectively.

b) Dopaminergic polymorphisms

None of the dopaminergic polymorphisms showed any statistically significant association with PCL-R Total scores (**Table 4.6**).

Polymorphism	χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
ANKK1 rs1800497	0.823	1	0.364	1
TH rs6356	0.044	1	0.834	1
DRD4 exonIII VNTR	2.677	1	0.102	1
DRD4 rs1800955	0.200	1	0.655	1
COMT rs4680	0.254	1	0.614	1
SLC6A3 3'UTR VNTR	5.674	1	1.7×10^{-2}	0.238

Table 4.6. Associations between the dopaminergic polymorphisms and PCL-R Total scores in incarcerated adults. Alpha level= 0.05/14 genetic variants= 0.0036.

c) Oxytocinergic polymorphisms

None of the oxytocinergic polymorphisms showed any statistically significant association with PCL-R Total scores (**Table 4.7**).

Polymorphism	χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
OXTR rs53576	0.016	1	0.900	1
OXTR rs1042778	2.377	1	0.123	1
OXTR rs237885	1.094	1	0.296	1

Table 4.7. Associations between the oxytocinergic polymorphisms and PCL-R Total scores in incarcerated adults. Alpha level= 0.05/14 genetic variants= 0.0036. df= degrees of freedom.

4.1.1.6 Genetic variants by paternal maltreatment by PCL-R interactions

a) Serotonergic polymorphisms

- ***5-HTR1B* rs13212041**

A significant interaction among *5-HTR1B* rs13212041, Paternal MOPS scores, and PCL-R Total scores (χ^2= 14.174, df= 2, $p_{value}= 2\times10^{-3}$, $p_{Bonf.}= 2.8\times10^{-2}$) was observed. Specifically, Paternal MOPS scores positively correlated with PCL-R Total scores in *5-HTR1B* rs13212041 T/T genotype carriers ($p_{value}= 1.84\times10^{-4}$, $p_{Bonf.}= 3.68\times10^{-4}$), but not in C allele carriers (p_{value}= 0.365, $p_{Bonf.}$= 0.730) (**Figure 4.3a**). More in details, the T/T genotype increased the variance of PCL-R Total scores explained by Paternal MOPS scores up to 7.4% (R^2= 0.080, $F_{1,145}$= 12.515, $p_{value}= 1\times10^{-2}$; β= 0.283; $\beta_{Latin/Hispanics}$= 0.298, $p_{value} < 0.05$, N= 86; $\beta_{not\text{-}Latin/Hispanics}$= 0.249, $p_{value} < 0.05$, N= 60).

Moreover, *5-HTR1B* rs13212041 and Paternal MOPS scores significantly interacted with both PCL-R Interpersonal/Affective (χ^2= 9.920, df= 2, $p_{value}= 7\times10^{-3}$, $p_{Bonf.}=$

1.4×10^{-2}) and Lifestyle/Antisocial (χ^2= 10.622, df= 2, p_{value}= 5×10^{-3}, $p_{Bonf.}$= 1×10^{-2}) scores. These correlations were statistically significant in *5-HTR1B* rs13212041 T/T genotype carriers (PCL-R Interpersonal/Affective: p= 6×10^{-3}, $p_{Bonf.}$= 1.2×10^{-2}, **Figure 4.3b**; PCL-R Lifestyle/Antisocial: p= 4×10^{-3}, $p_{Bonf.}$= 8×10^{-3}; **Figure 4.3c**), but not in C allele carriers (PCL-R Interpersonal/Affective: p= 0.484, $p_{Bonf.}$= 0.968; PCL-R Lifestyle/Antisocial: p_{value}= 0.682, $p_{Bonf.}$= 1). More in details, the T/T genotype increased the variance of PCL-R Interpersonal/Affective and Lifestyle/Antisocial scores explained by Paternal MOPS scores up to 6.4% (R^2= 0.070, $F_{1,145}$= 10.900, p_{value}= 0.01; β= 0.265; $\beta_{Latin/Hispanics}$= 0.276, $p_{value} < 0.05$, N= 86; $\beta_{not\text{-}Latin/Hispanics}$= 0.196, $p_{value} > 0.05$, N= 60) and 4% (R^2= 0.047, $F_{1,145}$= 7.069, p_{value}= 0.009; β= 0.216; $\beta_{Latin/Hispanics}$= 0.230, $p_{value} < 0.05$, N= 86; $\beta_{not\text{-}Latin/Hispanics}$= 0.214, $p_{value} > 0.05$, N= 60), respectively.

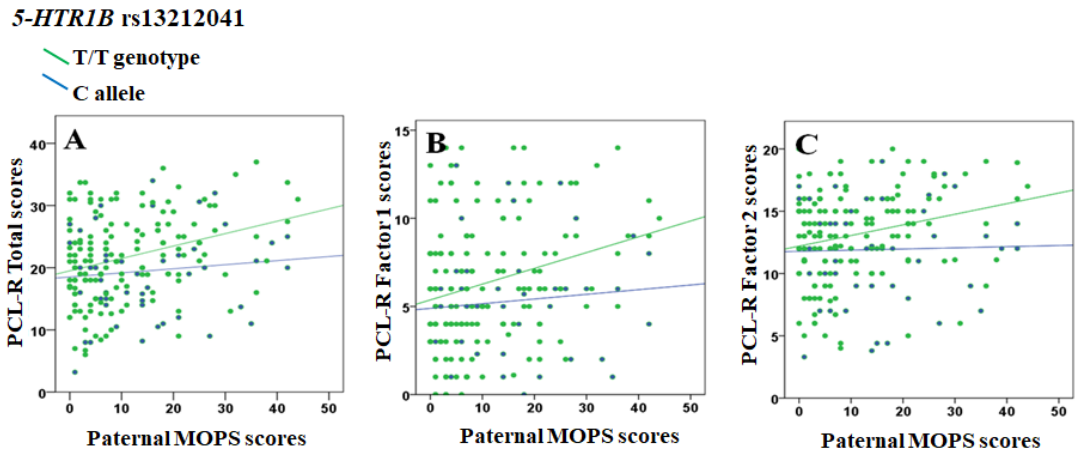

Figure 4.3. Correlations between Paternal MOPS scores and PCL-R Total scores divided by *5-HTR1B* rs13212041 genotype groupings in incarcerated adults. A) PCL-R Total, B) PCL-R Factor 1, and C) PCL-R Factor 2. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style. PCL-R Factor 1= Interpersonal/Affective, PCL-R Factor 2= Lifestyle/Antisocial

None of the other serotonergic polymorphisms showed any statistically significant interaction with Paternal MOPS scores and PCL-R scores (**Table 4.8**).

Polymorphism	χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
5-HTR1B rs13212041	14.174	2	2×10^{-3}	**2.8×10^{-2}**
MAOA uVNTR	10.715	2	1.4×10^{-2}	0.196
5-HTTLPR	8.980	2	2.2×10^{-2}	0.308
5-HTR2A rs6314	8.696	2	1.3×10^{-2}	0.182
TPH2 rs4570625	9.068	2	2.2×10^{-2}	0.308

Table 4.8. Interactions among the serotonergic polymorphisms, Paternal MOPS scores, and PCL-R Total scores in incarcerated adults. Alpha level= 0.05/14 genetic variants= 0.0036. df= degrees of freedom.

b) Dopaminergic polymorphisms

- ***ANKK1* rs1800497**

A significant interaction among *ANKK1* rs1800497, Paternal MOPS scores (χ^2= 14.757, df= 2, p= 2×10^{-3}, $p_{Bonf.}$= 2.8×10^{-2}), and PCL-R Total scores was observed. Specifically, Paternal MOPS scores positively correlated with PCL-R Total scores in *ANKK1* rs1800497 T allele carriers (p= 1.3×10^{-4}, $p_{Bonf.}$= 2.6×10^{-4}), but not in *ANKK1* rs1800497 C/C genotype carriers (p= 0.260, $p_{Bonf.}$= 0.520) (**Figure 4.4a**). More in details, the *ANKK1* rs1800497 T allele increased the variance of PCL-R Total scores explained by Paternal MOPS scores up to 10% (R^2= 0.108, $F_{1,113}$= 13.571, p= 3.6×10^{-4}; β= 0.329; $\beta_{Latin/Hispanics}$= 0.407, $p_{value} < 0.05$, N= 73; $\beta_{not\text{-}Latin/Hispanics}$= 0.207, $p_{value} > 0.05$, N= 41).

Moreover, *ANKK1* rs1800497 and Paternal MOPS scores significantly interacted with PCL-R Interpersonal/Affective scores (χ^2= 11.698, df= 2, p_{value}= 3×10^{-3}, $p_{Bonf.}$= 6×10^{-3}), but not with PCL-R Lifestyle/Antisocial scores (χ^2= 7.271, df= 2, p_{value}= 2.6×10^{-2}, $p_{Bonf.}$= 0.104). This correlation was statistically significant in *ANKK1* rs1800497 T allele carriers (p= 1.2×10^{-2}, $p_{Bonf.}$= 2.4×10^{-2}) (**Figure 4.4b**), but not in *ANKK1* rs1800497 C/C genotype carriers (p= 0.205, $p_{Bonf.}$= 0.410). More in details, the *ANKK1* rs1800497 T allele increased the variance of PCL-R Interpersonal/Affective scores explained by Paternal MOPS scores up to 9% (R^2= 0.098, $F_{1,113}$= 12.338, p_{value}= 1×10^{-3}; β= 0.314; $\beta_{Latin/Hispanics}$= 0.384, $p_{value} < 0.05$, N= 73; $\beta_{not\text{-}Latin/Hispanics}$= 0.201, $p_{value} > 0.05$, N= 41).

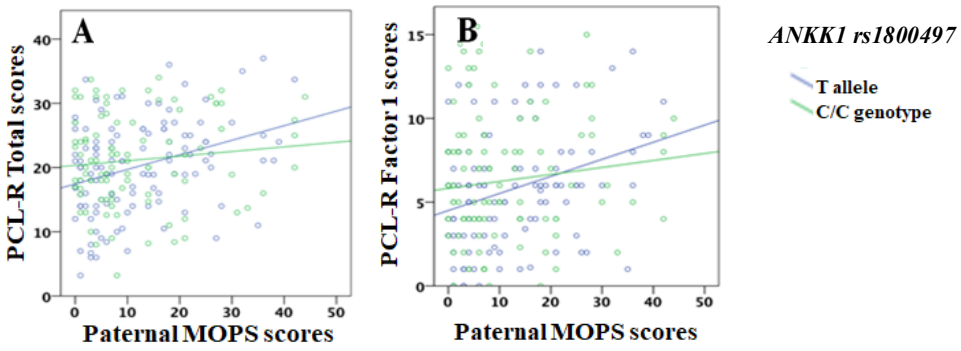

Figure 4.4. Correlations between Paternal MOPS scores and PCL-R scores divided by *ANKK1* rs1800497 genotype groupings in incarcerated adults. A) PCL-R Total and B) PCL-R Factor 1. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style. PCL-R Factor 1= Interpersonal/Affective, PCL-R Factor 2= Lifestyle/Antisocial

- ***TH* rs6353**

  A significant interaction among *TH* rs6356, Paternal MOPS scores, and PCL-R Total scores (χ^2= 14.203, df= 2, p= 2×10^{-3}, $p_{Bonf.}$= 2.8×10^{-2}) was observed.

  Specifically, Paternal MOPS scores positively correlated with PCL-R Total scores in in *TH* rs6356 G/G genotype carriers (p= 1.3×10^{-2}, $p_{Bonf.}$= 2.6×10^{-2}), but not in *TH* rs6356 A allele carriers (p= 0.038, $p_{Bonf.}$= 0.076) (**Figure 4.5a**). More in details, the *TH* rs6356 G/G genotype increased the variance of PCL-R Total scores explained by Paternal MOPS scores up to 13.9% (R^2= 0.153, $F_{1,63}$= 11.193, p= 1×10^{-3}; β= 0.391; $\beta_{Latin/Hispanics}$= 0.546, p_{value} < 0.05, N= 28; $\beta_{not\text{-}Latin/Hispanics}$= 0.330, p_{value} < 0.05, N= 36). Moreover, *TH* rs6356 and Paternal MOPS scores significantly interacted with PCL-R Interpersonal/Affective (χ^2= 18.932, df= 2, p= 7×10^{-3}, $p_{Bonf.}$= 2.8×10^{-4}), but not with Lifestyle/Antisocial scores (χ^2= 7.659, df= 2, p_{value}= 0.022, $p_{Bonf.}$= 0.088). This correlation was statistically significant in *TH* rs6356 G/G genotype carriers (p= 9×10^{-5}, $p_{Bonf.}$= 1.8×10^{-4}) (**Figure 4.5b**), but not in *TH* rs6356 A allele carriers (p= 0.060, $p_{Bonf.}$= 0.120). More in details, the *TH* rs6356 G/G genotype increased the variance of PCL-R Interpersonal/Affective scores explained by Paternal MOPS scores up to 13.7% (R^2= 0.154, $F_{1,64}$= 11.501, p_{value}= 1×10^{-3}; β= 0.389; $\beta_{Latin/Hispanics}$= 0.355, p_{value} < 0.05, N= 28; $\beta_{not\text{-}Latin/Hispanics}$= 0.351, p_{value} > 0.05, N= 36).

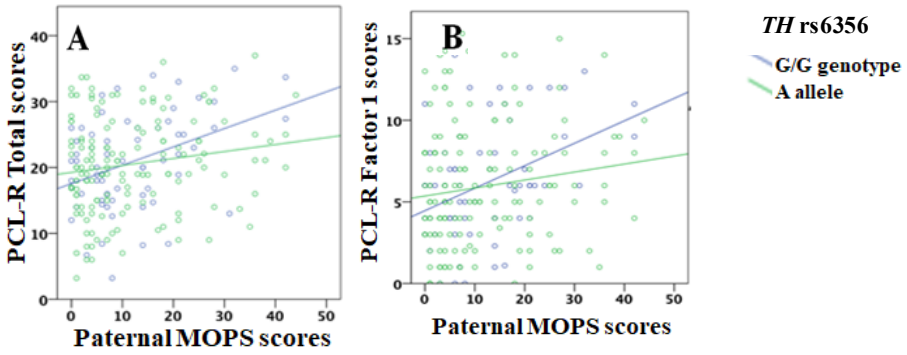

Figure 4.4.Correlations between Paternal MOPS scores and PCL-R scores divided by *TH* rs6356 genotype groupings in incarcerated adults. A) PCL-R Total and B) PCL-R Factor 1. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style.PCL-R Factor 1= interpersonal/affective, PCL-R Factor 2= lifestyle/antisocial

None of the other dopaminergic polymorphisms showed any statistically significant interaction with Paternal MOPS scores and PCL-R scores (**Table 4.9**).

Polymorphisms	χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
ANKK1 rs1800497	14.757	2	2×10^{-3}	**2.8×10^{-2}**
TH rs6356	14.203	2	2×10^{-3}	**2.8×10^{-2}**
DRD4 exonIII VNTR	8.462	2	1.5×10^{-2}	0.210
DRD4 rs1800955	10.335	2	6×10^{-3}	0.084
SLC6A3 3'UTR VNTR	10.499	2	5.3×10^{-3}	0.074
COMT rs4680	10.717	2	5×10^{-3}	0.070

Table 4.9. Interactions among the dopaminergic polymorphisms, Paternal MOPS scores, and PCL-R Total scores in incarcerated adults. Alpha level= 0.05/14 genetic variants= 0.0036. df= degrees of freedom.

c) Oxytocinergic polymorphisms

- *OXTR* 53576

A significant interaction among the *OXTR* rs53576, Paternal MOPS scores, and PCL-R Total scores was observed (χ^2= 12.422, df= 2, p= 3.5×10^{-3}, $p_{Bonf.}$= 4.9×10^{-2}). Specifically, Paternal MOPS scores positively correlated with PCL-R Total scores in *OXTR* rs53576 A allele carriers (p= 1×10^{-3}, $p_{Bonf.}$= 2×10^{-3}), but not in G/G genotype carriers (p= 0.191, $p_{Bonf.}$= 0.382) (**Figure 4.5a**). More in details,the A allele increased the variance of PCL-R Total scores explained by Paternal MOPS scores up to 7.3% (R^2= 0.081, $F_{1,118}$= 10.266, p_{value}= 0.002; β= 0.284; $\beta_{Latin/Hispanics}$= 0.334, $p_{value} < 0.05$, N= 67; $\beta_{not\text{-}Latin/Hispanics}$= 0.228, $p_{value} > 0.05$, N= 52).

Moreover, *OXTR* rs53576 and Paternal MOPS scores significantly interacted with both PCL-R Interpersonal/Affective (χ^2= 10.702, df= 2, p= 2×10^{-3}, $p_{Bonf.}$= 4×10^{-3}) and Lifestyle/Antisocial (χ^2= 12.343, df= 2, p= 3×10^{-3}, $p_{Bonf.}$= 4×10^{-3}) scores. Specifically, these correlations were statistically significant in *OXTR* rs53576 A allele carriers (PCL-R interpersonal/affective: p= 3×10^{-3}, $p_{Bonf.}$= 6×10^{-3};**Figure 4.5b**; PCL-R lifestyle/antisocial: p= 1.2×10^{-3}, $p_{Bonf,}$= 2.4×10^{-3}; **Figure 4.5c**), but not in G/G genotype carriers (PCL-R Interpersonal/Affective: p_{value}= 0.115, $p_{Bonf.}$= 0.596; PCL-R Lifestyle/Antisocial: p_{value}= 0.792, $p_{Bonf.}$= 1). More in details, the A allele increased the variance of PCL-R Interpersonal/Affective and Lifestyle/Antisocial scores explained by Paternal MOPS scores up to 5% (R^2= 0.058, $F_{1,122}$= 7.528, p_{value}= 0.021; β= 0.241; $\beta_{Latin/Hispanics}$= 0.315, $p_{value} < 0.05$, N= 67; $\beta_{not\text{-}Latin/Hispanics}$= 0.162, $p_{value} > 0.05$, N= 52) and 5.3% (R^2= 0.06, $F_{1,122}$= 7.831, p_{value}= 0.018; β= 0.246; $\beta_{Latin/Hispanics}$= 0.258, $p_{value} < 0.05$, N= 67; $\beta_{not\text{-}Latin/Hispanics}$= 0.207, $p_{value} > 0.05$, N= 52), respectively.

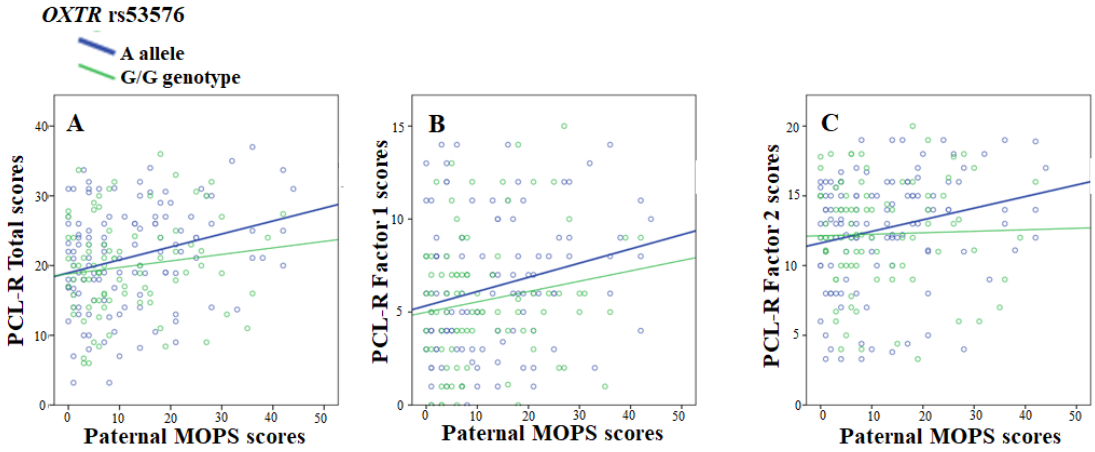

Figure 4.5. Correlations between Paternal MOPS scores, and PCL-R scores divided by *OXTR* rs53576 genotype groupings in incarcerated adults. A) PCL-R Total, B) PCL-R Factor 1, and C) PCL-R Factor 2. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style. PCL-R Fatcor 1= interpersonal/affective, PCL-R Factor 2= lifestyle/antisocial

None of the other dopaminergic polymorphisms showed any statistically significant interaction with Paternal MOPS scores and PCL-R scores (**Table 4.10**).

Polymorphisms	χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
OXTR rs53576	12.422	2	3.5×10^{-3}	**4.9×10^{-2}**
OXTR rs1042778	10.328	2	6×10^{-3}	0.084
OXTR rs237885	8.612	2	1.3×10^{-2}	0.182

Table 4.10. Interactions among oxytocinergic polymorphisms, Paternal MOPS scores and PCL-R Total scores in incarcerated adults. Alpha level= 0.05/14 genetic variants= 0.0036. df= degrees of freedom.

4.1.1.7 Moderation analysis of *5-HTR1B* rs13212041 on the correlation between Paternal MOPS scores and PCL-R scores

A significant moderating effect of *5-HTR1B* rs13212041 on the correlation between PCL-R Total scores and Paternal MOPS scores emerged (t_{218}= 2.088, p_{value}= 3.9×10^{-2}, 95% CI: 0.013 – 0.467; F= 4.358, R^2= 0.029). Specifically, individuals with the T/T genotype showed a greater effect of the focal predictor (Paternal MOPS score) on PCL-R Total score (t_{153}= 2.933, p_{value}= 4×10^{-3}, 95% CI: 0.064 – 0.331) compared to those with the C allele (t_{65}= 0.434, p_{value}= 0.665, 95% CI: -0.232 – 0.149).

Moreover, a significant moderating effect of *5-HTR1B* rs13212041 on the correlation between PCL-R Interpersonal/Affective scores and Paternal MOPS scores emerged (t_{218}= 2.056, p_{value}= 4.2×10^{-2}, 95% CI: 0.004 – 0.230; F= 4.229, R^2= 0.028). Specifically, individuals with the T/T genotype showed a greater effect of the focal predictor (Paternal MOPS score) on PCL-R

Interpersonal/Affective score (t_{153}= 2.902, p_{value}= 4×10^{-3}, 95% CI: 0.031 – 0.163) compared to those with the C allele (t_{65}= 0.418, p_{value}= 0.676, 95% CI: -0.115 – 0.075).

Moreover, a significant moderating effect of *5-HTR1B* rs13212041 on the correlation between PCL-R Lifestyle/Antisocial scores and Paternal MOPS scores emerged (t_{218}= 2.020, p_{value}= 4.5×10^{-2}, 95% CI: 0.003 – 0.259; F= 4.081, R^2= 0.028). Specifically, individuals with the T/T genotype showed a greater effect of the focal predictor (Paternal MOPS score) on PCL-R Lifestyle/Antisocial score (t_{153}= 2.204, p_{value}= 2.9×10^{-2}, 95% CI: 0.009 – 0.168) compared to those with the C allele (t_{65}= 0.794, p_{value}= 0.428, 95% CI: -0.149 – 0.064).

4.1.1.8 Effects of gene-by-gene interactions on the correlations between Paternal MOPS scores and PCL-R scores

a) **PCL-R Total**

A gene-by-gene interaction analysis was performed among the genetic variants (i.e., *5-HTR1B* rs13212041, *ANKK1* rs1800497, *TH*-rs6356, and *OXTR* rs53576) that significantly influenced the correlation between Paternal MOPS scores and PCL-R Total scores (see **4.1.1.6**). Results are reported in **Table 4.11**.

Gene-by-gene interactions	χ^2	df	p_{value}	$p_{Bonferroni-correction}$
5-HTR1B rs13212041 by *ANKK1* rs1800497	17.872	4	1×10^{-3}	**6×10^{-3}**
5-HTR1B rs13212041 by *TH* rs6356	17.245	4	2×10^{-3}	**1.2×10^{-2}**
5-HTR1B rs13212041 by *OXTR* rs53576	25.815	4	3×10^{-5}	**1.8×10^{-4}**
ANKK1 rs1800497 by *OXTR* rs53576	17.886	4	1×10^{-3}	**6×10^{-3}**
ANKK1 rs1800497 by *TH* rs6356	24.09	4	8×10^{-4}	**4.8×10^{-3}**
OXTR rs53576 by *TH* rs6356	21.284	4	3×10^{-4}	**1.8×10^{-3}**
5-HTR1B rs13212041 by *ANKK1* rs1800497 by *TH* rs6356	26.931	8	1×10^{-3}	**3×10^{-3}**
5-HTR1B rs13212041 by *ANKK1* rs1800497 by *OXTR* rs53576	30.553	8	2×10^{-4}	**6×10^{-4}**
5-HTR1B rs13212041 by *TH* rs6356 by *OXTR* rs53576	35.933	8	2×10^{-4}	**6×10^{-4}**
ANKK1 rs1800497 by *TH* rs6356 by *OXTR* rs53576	not performed due to the low number of individuals carrying the combination of all the three risk genotypes (i.e., *ANKK1* rs1800497 T allele, *TH* rs6356 G/G genotype, and *OXTR* rs53576 A allele; N=14)			

Table 4.11. Influence of the gene-by-gene interactions on the correlations between Paternal MOPS scores and PCL-R Total scores. Alpha level= 0.05/6 interactions between two genetic variants= 0.0083. Alpha level= 0.05/3 interactions among three genetic variants = 0.017.df= degrees of freedom.

In details, the correlation between Paternal MOPS scores and PCL-R Total scores was significantly influenced by the following combinations of genotypes (see **Table 4.12**):

- ***5-HTR1B* rs13212041 T/T genotype and *ANKK1* rs1800497 T allele** (χ^2= 15.225, df= 1, p_{value}= 9.4×10^{-5}, $p_{Bonf.}$= 2.3×10^{-3}; **Figures 4.6** and **4.7**), which increased up to 16.2% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.172, $F_{1,80}$= 16.416, p_{value}= 1.18×10^{-4}; β= 0.415; $\beta_{Latin/Hispanics}$= 0.386, p_{value} < 0.05, N= 55; $\beta_{not\text{-}Latin/Hispanics}$= 0.475, p_{value} < 0.05, N= 26).

  ***5-HTR1B* rs13212041 T/T genotype and *TH* rs6356 G/G genotype** (χ^2= 11.400, df= 1, p_{value}= 1×10^{-3}, $p_{Bonf.}$= 2.4×10^{-2}; **Figures 4.6** and **4.8**), which increased up to 15.3% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.173, $F_{1,43}$= 8.581, p_{value}= 6×10^{-3}; β= 0.416; $\beta_{Latin/Hispanics}$= 0.522, p_{value} < 0.05, N= 21; $\beta_{not\text{-}Latin/Hispanics}$= 0.362, p_{value} > 0.05, N= 21).

- ***5-HTR1B* rs13212041 T/T genotype and *OXTR* rs53576 A allele** (χ^2= 15.022, df= 1, p_{value}= 1×10^{-4}, $p_{Bonf.}$= 2.4×10^{-2}; **Figures 4.7** and **4.8**), which increased up to 11.7% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.127, $F_{1,89}$= 12.821, p_{value}= 1×10^{-3}; β= 0.357; $\beta_{Latin/Hispanics}$= 0.411, p_{value} < 0.05, N= 51; $\beta_{not\text{-}Latin/Hispanics}$= 0.301, p_{value} > 0.05, N= 39).

- ***ANKK1* rs1800497 T allele and *OXTR* rs53576 A allele** (χ^2= 12.281, df= 1, p_{value}= 5×10^{-4}, $p_{Bonf.}$= 1.2×10^{-2}; **Figure 4.7**), which increased up to 16.1% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.175, $F_{1,60}$= 12.553, p_{value}= 1×10^{-3}; β= 0.419; $\beta_{Latin/Hispanics}$= 0.517, p_{value} < 0.05, N= 39; $\beta_{not\text{-}Latin/Hispanics}$= 0.252, p_{value} < 0.05, N= 21).

- ***ANKK1* rs1800497 T allele and *TH* rs6356 G/G genotype** (χ^2= 20.259, df= 1, p_{value}= 7×10^{-6}, $p_{Bonf.}$= 1.7×10^{-4}; **Figure 4.6**), which increased up to 35.4% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.377, $F_{1,28}$= 16.365, p_{value}= 5.75×10^{-4}; β= 0.614; $\beta_{Latin/Hispanics}$= 0.731, p_{value} < 0.05, N= 13; $\beta_{not\text{-}Latin/Hispanics}$= 0.521, p_{value} < 0.05, N= 15).

- ***OXTR* rs53576 A allele and *TH* rs6356 G/G genotype** (χ^2= 16.253, df= 1, p_{value}= 6×10^{-5}, $p_{Bonf.}$= 1.4×10^{-3}; **Figure 4.8**), which increased up to 22.1% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.243, $F_{1,35}$= 10.932, p_{value}= 2×10^{-3}; β= 0.493; $\beta_{Latin/Hispanics}$= 0.726, p_{value} < 0.05, N= 15; $\beta_{not\text{-}Latin/Hispanics}$= 0.381, p_{value} > 0.05, N= 19).

- ***5-HTR1B* rs13212041 T/T genotype, *ANKK1* rs1800497 T allele, and *TH* rs6356 G/G genotype** (χ^2= 20.026, df= 1, $p_{value}< 10^{-6}$, $p_{Bonf.}< 10^{-6}$; **Figure 4.6**), which increased up to 43% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.459, $F_{1,20}$= 16.111, $p_{value}= 1\times10^{-3}$; β= 0.677; $\beta_{Latin/Hispanics}$= 0.730, $p_{value} < 0.05$, N= 12; $\beta_{not\text{-}Latin/Hispanics}$= 0.381, $p_{value} > 0.05$, N= 9).

- ***5-HTR1B* rs13212041 T/T genotype, *TH* rs6356 G/G genotype, and *OXTR* rs53576 A allele** (χ^2= 16.541, df= 1, $p_{value}= 5\times10^{-5}$, $p_{Bonf.}= 1.2\times10^{-3}$; **Figure 4.7**), which increased up to 39.4% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.444, $F_{1,24}$= 16.616, $p_{value}= 5\times10^{-4}$; β= 0.648; $\beta_{Latin/Hispanics}$= 0.667, $p_{value} < 0.05$, N= 12; $\beta_{not\text{-}Latin/Hispanics}$= 0.623, $p_{value} < 0.05$, N= 13).

- ***5-HTR1B* rs13212041 T/T genotype, *ANKK1* rs1800497 T allele, and *OXTR* rs53576 A allele** (χ^2= 25.710, df= 1, $p_{value}< 10^{-6}$, $p_{Bonf.}< 10^{-6}$; **Figure 4.8**), which increased up to 18% the variance of PCL-R Total scores explained by Paternal MOPS scores (R^2= 0.197, $F_{1,47}$= 11.288, $p_{value}= 2\times10^{-3}$; β= 0.444; $\beta_{Latin/Hispanics}$= 0.499, $p_{value} < 0.05$, N= 32; $\beta_{not\text{-}Latin/Hispanics}$= 0.364, $p_{value} > 0.05$, N= 16).

None of the other combinations of genotypes significantly influenced the correlation between Paternal MOPS scores and PCL-R Total scores (**Table 4.12**).

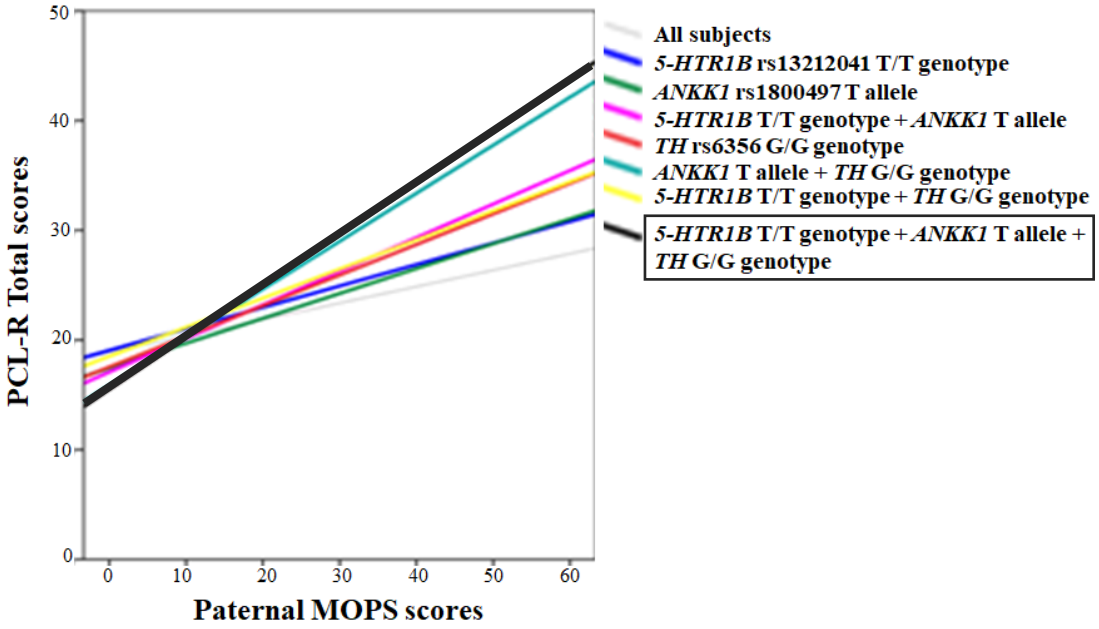

Figure 4.6. Correlations between Paternal MOPS scores and PCL-R Total scores for the *5-HTR1B* rs13212041 T/T genotype by *ANKK1* rs1800497 T allele by *TH* rs6356 G/G genotype interaction. *5-HTR1B* rs13212041 T/T genotype + *ANKK1* rs1800497 T allele + *TH* rs6356 G/G (β= 0.677, black line), as compared to any genotype (β= 0.225, grey line), *5-HTR1B* rs13212041 T/T genotype (β= 0.283, blue line), *ANKK1* rs1800497 T allele (β= 0.329, green line), *TH* rs6356 G/G genotype (β= 0.391, red line), *5-HTR1B* rs13212041 T/T genotype + *ANKK1* rs1800497 T allele (β= 0.415, pink line), *ANKK1* rs1800497 T allele + *TH* rs6356 G/G genotype (β= 0.614, light blue line), *5-HTR1B* rs13212041 T/T genotype + *TH* rs6356 G/G genotype (β= 0.413, yellow line). PCL-R= Psychopathy Checklist-revised, MOPS= Measure of Parental Style.

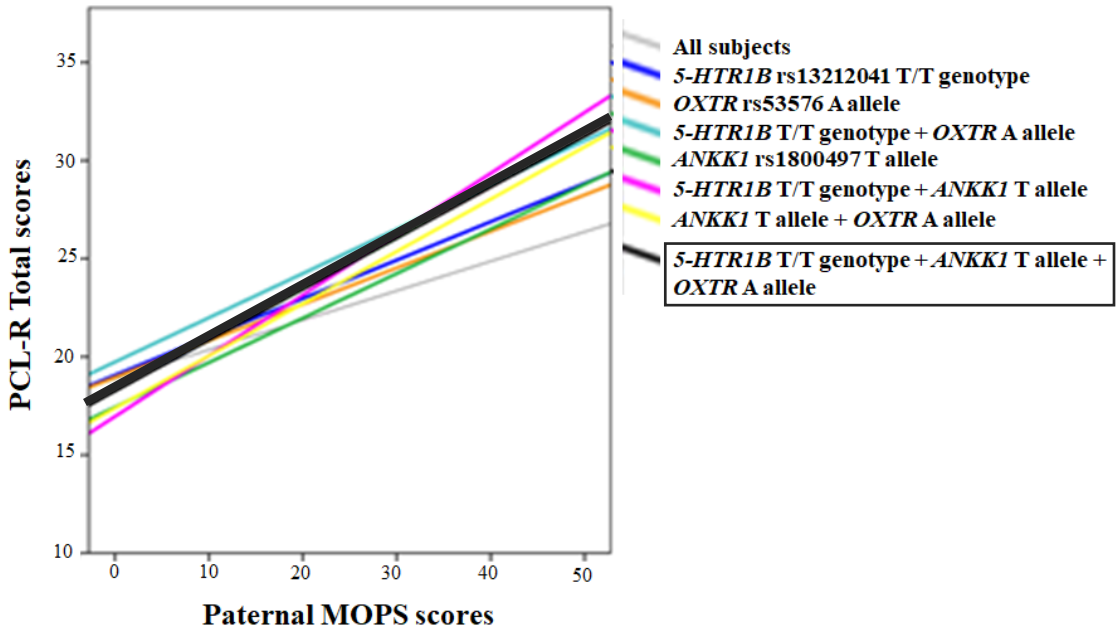

Figure 4.7. Correlations between Paternal MOPS scores and PCL-R Total scores for the *5-HTR1B* rs13212041 T/T genotype by *ANKK1* rs1800497 T allele by *OXTR* rs53576 A allele interaction. *5-HTR1B* rs13212041 T/T genotype + *ANKK1* rs1800497 T allele + *OXTR* rs53576 G/G genotype (β= 0.444, black line), as compared to any genotype (β= 0.225, grey line), *5-HTR1B* rs13212041 T/T genotype (β= 0.283, blue line), *ANKK1* rs1800497 T allele (β= 0.329, green line), *OXTR* rs53576 A allele (β= 0.284, orange line), *5-HTR1B* rs13212041 T/T genotype + ANKK1 rs1800497 T allele (β= 0.415, pink line), *5-HTR1B* rs13212041 T/T genotype + *OXTR* rs53576 A allele (β= 0.357, light blue line), and *ANKK1* rs1800497 T allele + *OXTR* rs53576 A allele (β= 0.419, yellow line). PCL-R= Psychopathy Checklist-revised, MOPS= Measure of Parental Style.

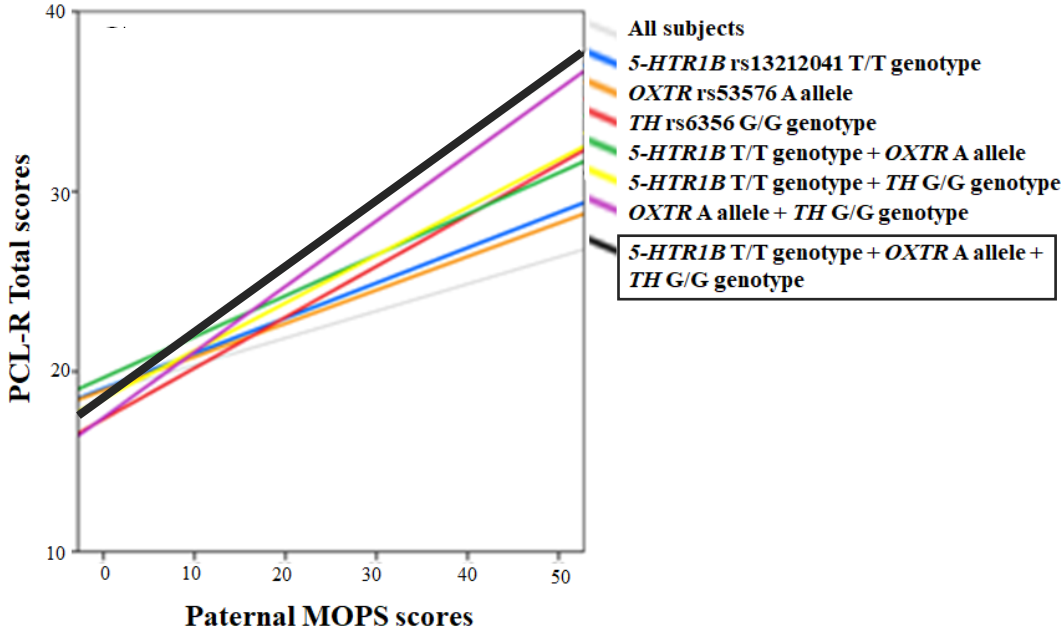

Figure 4.8. Correlations between Paternal MOPS scores and PCL-R Total scores for the *5-HTR1B* rs13212041 T/T genotype by *OXTR* rs53576 A allele by *TH* rs6356 G/G genotype interaction. *5-HTR1B* rs13212041 T/T genotype + *OXTR* rs53576 A allele + *TH* rs6356 G/G genotype (β= 0.648, black line) as compared to any genotype (β= 0.225, grey line), *5-HTR1B* rs13212041 T/T genotype (β= 0.283, blue line), *OXTR* rs53576 A allele (β= 0.284, orange line), *TH* rs6356 G/G genotype (β= 0.391, red line), *5-HTR1B* rs13212041 T/T genotype + *OXTR* rs53576 A allele (β= 0.357, green line), *5-HTR1B* rs13212041 T/T genotype + *TH* rs6356 G/G genotype (β= 0.413, yellow line), *OXTR* rs53576 A allele + *TH* rs6356 G/G genotype (β= 0.493, violet line). PCL-R= Psychopathy Checklist-revised, MOPS= Measure of Parental Style.

Gene-by-gene interactions			**Paternal MOPS by PCL-R Total correlations**			
Combinations of genotypes			χ^2	df	p_{value}	$p_{Bonferroni-corrected}$
***5-HTR1B* rs13212041**		***ANKK1* rs1800497**				
T/T genotype	+	T allele	15.225	1	9.4×10^{-5}	$\mathbf{2.3\times10^{-3}}$
C allele	+	C/C genotype	0.113	1	0.737	1
T/T genotype	+	C/C genotype	1.989	1	0.158	1
C allele	+	T allele	2.586	1	0.108	1
***5-HTR1B* rs13212041**		***TH* rs6356**				
T/T genotype	+	G/G genotype	11.400	1	1×10^{-3}	$\mathbf{2.4\times10^{-2}}$
C allele	+	A allele	0.663	1	0.415	1
C allele	+	G/G genotype	1.503	1	0.220	1
T/T genotype	+	A allele	4.990	1	2.5×10^{-2}	0.6
***5-HTR1B* rs13212041**		***OXTR rs53576***				
T/T genotype	+	A allele	11.400	1	1×10^{-3}	$\mathbf{2.4\times10^{-2}}$
C allele	+	A allele	0.385	1	0.535	1
C allele	+	G/G genotype	2.675	1	0.102	1
T/T genotype	+	G/G genotype	1.081	1	0.313	1
***ANKK1* rs1800497**		***OXTR rs53576***				
T allele		+A allele	12.281	1	5×10^{-4}	$\mathbf{1.2\times10^{-2}}$
C/C genotype	+	A allele	2.559	1	0.110	1
C/C genotype	+	G/G genotype	0.185	1	0.667	1
T allele		+G/G genotype	2.656	1	0.103	1
***ANKK1* rs1800497**		***TH* rs6356**				
T allele		+G/G genotype	20.259	1	7×10^{-6}	$\mathbf{1.7\times10^{-4}}$
C/C genotype		+G/G genotype	1.432		0.233	1

C/C genotype +A allele	0.945	1	0.331	1
T allele +A allele	6.360	1	1.7×10^{-2}	0.408
OXTR rs53576 + ***TH* rs6356**				
A allele + G/G genotype	16.253	1	6×10^{-5}	**1.4×10^{-3}**
A allele + A allele	4.675	1	3.1×10^{-2}	0.744
G/G genotype + G/G genotype	2.805	1	0.094	1
G/G genotype + A allele	0.521	1	0.470	1
5-HTR1B rs13212041 + *ANKK1* rs1800497 + *TH* rs6356				
T/T genotype + T allele + G/G genotype	20.026	1	$< 10^{-6}$	**$< 10^{-6}$**
C allele + C/C genotype + G/G genotype	0.017	1	0.897	1
C allele + C/C genotype + A allele	0.136	1	0.712	1
C allele + T allele + G/G genotype	4.288	1	3.8×10^{-2}	0.912
C allele + T allele + A allele	1.537	1	0.215	1
T/T genotype + C/C genotype + G/G genotype	1.644	1	0.200	1
T/T genotype + C/C genotype + A allele	0.913	1	0.339	1
T/T genotype + T allele + A allele	7.061	1	8×10^{-3}	0.192
5-HTR1B rs13212041 + *TH* rs6356 + *OXTR rs53576*				
T/T genotype + G/G genotype + A allele	16.541	1	5×10^{-5}	**1.2×10^{-3}**
C allele + G/G genotype + G/G genotype	0.063	1	0.802	1
C allele + G/G genotype + A allele	2.743	1	0.098	1
C allele + A allele + A allele	0.272	1	0.602	1
C allele + A allele + G/G genotype	2.819	1	0.093	1
T/T genotype + G/G genotype + G/G genotype	1.776	1	0.183	1
T/T genotype + A allele + A allele	6.971	1	8×10^{-3}	0.192
T/T genotype + G/G genotype + A allele	0.009	1	0.923	1
5-HTR1B rs13212041 + *ANKK1* rs1800497 + *OXTR rs53576*				
T/T genotype + T allele + A allele	25.710	1	$< 10^{-6}$	**$< 10^{-6}$**
C allele + C/C genotype + A allele	0.006	1	0.937	1
C allele + T allele + A allele	1.162	1	0.281	1
C allele + C/C genotype + G/G genotype	2.060	1	0.151	1
C allele + T allele + G/G genotype	3.243	1	0.072	1
T/T genotype + C/C genotype + A allele	6.741	1	9×10^{-3}	0.216
T/T genotype. + C/C genotype + G/G genotype	0.022	1	0.883	1
T/T genotype + T allele + G/G genotype	2.032	1	0.154	1

Table 4.12. Influence of the gene-by-gene interactions on the correlation between Paternal MOPS scores and PCL-R Total scores. Alpha level= 0.05/24 combinations of genotypes = 0.002. PCL-R= Psychopathy Checklist-Revised, MOPS= Measure of Parental Style.

The analysis of interaction among all the four genetic variants (i.e., *5-HTR1B* rs13212041, *ANKK1* rs1800497, *TH* rs6356, and *OXTR* rs53576) was not performed due to the low number of subjects carrying all the four risk alleles (*5-HTR1B* rs13212041 T/T genotype, *ANKK1* rs1800497 T allele, *TH* rs6356 G/G genotype,and *OXTR* rs53576 A allele; N= 12).

b) PCL-R Interpersonal/Affective

A gene-by-gene interaction analysis was performed among the genetic variants (i.e., *5-HTR1B* rs13212041, *ANKK1* rs1800497, *TH*-rs6356, and *OXTR* rs53576) that significantly influenced

the correlation between Paternal MOPS scores and PCL-R Interpersonal/Affective scores (see **4.1.1.6**). Results are reported in **Table 4.13**.

Gene-by-gene interactions	χ^2	df	p_{value}	$p_{Bonferroni-correction}$
5-HTR1B rs13212041 by *ANKK1* rs1800497	15.179	4	4×10^{-3}	**2.8×10^{-2}**
5-HTR1B rs13212041 by *TH* rs6356	16.417	4	3×10^{-3}	**2.1×10^{-2}**
5-HTR1B rs13212041 by *OXTR* rs53576	23.491	4	1×10^{-4}	**7×10^{-4}**
ANKK1 rs1800497 by *OXTR* rs53576	12.163	4	1.6×10^{-2}	0.216
ANKK1 rs1800497 by *TH* rs6356	14.563	4	6×10^{-3}	0.072
OXTR rs53576 by *TH* rs6356	14.471	4	6×10^{-3}	0.072
5-HTR1B rs13212041 by *ANKK1* rs1800497 by *TH* rs6356	19.873	8	1.1×10^{-2}	**3.3×10^{-2}**
5-HTR1B rs13212041 by *TH* rs6356 by *OXTR* rs53576	31.788	8	6×10^{-4}	**1.8×10^{-3}**
5-HTR1B rs13212041 by *ANKK1* rs1800497 by *OXTR* rs53576	26.517	8	1×10^{-3}	**3×10^{-3}**

Table 4.13. Influence of the gene-by-gene interactions on the correlation between Paternal MOPS scores and interpersonal/affective scores. Alpha level= 0.05/7 interactions between two genetic variants for both PCL-R interpersonal/affective and lifestyle/antisocial= 0.0071. Alpha level= 0.05/3 interactions among three genetic variants= 0.017. df= degrees of freedom.

In details, the correlation between Paternal MOPS scores and PCL-R Interpersonal/Affective scores was significantly influenced by the following combinations of genotypes (see **Table 4.14**):

- ***5-HTR1B* rs13212041 T/T genotype and *ANKK1* rs1800497 T allele** (χ^2= 9.006, df= 1, $p_{value}= 3\times10^{-3}$, $p_{Bonf.}= 3.6\times10^{-2}$; **Figures 4.9**), which increased up to 11.5% the variance of PCL-R interpersonal/affective scores explained by Paternal MOPS scores (R^2= 0.126, $F_{1,80}$= 11.361, $p_{value}= 1\times10^{-3}$; β= 0.355; $\beta_{Latin/Hispanics}$= 0.355, $p_{value} < 0.05$, N= 54; $\beta_{not-Latin/Hispanics}$= 0.379, $p_{value} > 0.05$, N= 26).

- ***5-HTR1B* rs13212041 T/T genotype and *TH* rs6356 G/G genotype** (χ^2= 11.722, df= 1, $p_{value}= 1\times10^{-3}$, $p_{Bonf.}= 1.2\times10^{-2}$; **Figure 4.10**), which increased up to 13.4% the variance of PCL-R interpersonal/affective scores explained by Paternal MOPS scores (R^2= 0.154, $F_{1,42}$= 8.910, $p_{value}= 9\times10^{-3}$; β= 0.393; $\beta_{Latin/Hispanics}$= 0.332, $p_{value} > 0.05$, N= 21; $\beta_{not-Latin/Hispanics}$= 0.396, $p_{value} > 0.05$, N= 22).

- ***5-HTR1B* rs13212041 T/T genotype and *OXTR* rs53576 A allele** (χ^2= 15.022, df= 1, $p_{value}= 1\times10^{-4}$, $p_{Bonf.}= 1.2\times10^{-3}$; **Figures 4.9** and **4.10**), which increased up to 7.7% the variance of PCL-R interpersonal/affective scores explained by Paternal MOPS scores (R^2=

0.088, $F_{1,89}$= 8.910, p_{value}= 5×10^{-3}; β= 0.296; $\beta_{Latin/Hispanics}$= 0.399, p_{value} < 0.05, N= 51; $\beta_{not\text{-}Latin/Hispanics}$= 0.203, p_{value} > 0.05, N= 39).

- ***5-HTR1B* rs13212041 T/T genotype, *TH* rs6356 G/G genotype, and *OXTR* rs53576 A allele** (χ^2= 11.718, df= 1, p_{value}= 1×10^{-3}, $p_{Bonf.}$= 2.4×10^{-2}; **Figures 4.9**), which increased up to 14.1%the variance of PCL-R interpersonal/affective scores explained by Paternal MOPS scores (R^2= 0.159, $F_{1,24}$= 8.703, p_{value}= 5x10^{-3}; β= 0.399; $\beta_{Latin/Hispanics}$= 0.296, p_{value} > 0.05, N= 12; $\beta_{not\text{-}Latin/Hispanics}$= 0.580, p_{value} < 0.05, N= 13).

- ***5-HTR1B* rs13212041 T/T genotype, *ANKK1* rs1800497 T allele and *OXTR* rs53576 A allele** (χ^2= 13.431, df= 1, p_{value}= 3×10^{-4}, $p_{Bonf.}$= 7.2×10^{-3}; **Figures 4.10**), which increased up to 14.5% the variance of PCL-R interpersonal/affective scores explained by Paternal MOPS scores (R^2= 0.181, $F_{1,47}$= 5.085, p_{value}= 3.4×10^{-2}; β= 0.425; $\beta_{Latin/Hispanics}$= 0.516, p_{value} < 0.05, N= 31; $\beta_{not\text{-}Latin/Hispanics}$= 0.296, p_{value} > 0.05, N= 15).

None of the other combinations of genotypes significantly influenced the correlation between Paternal MOPS scores and PCL-R interpersonal/affective scores (**Table 4.14**).

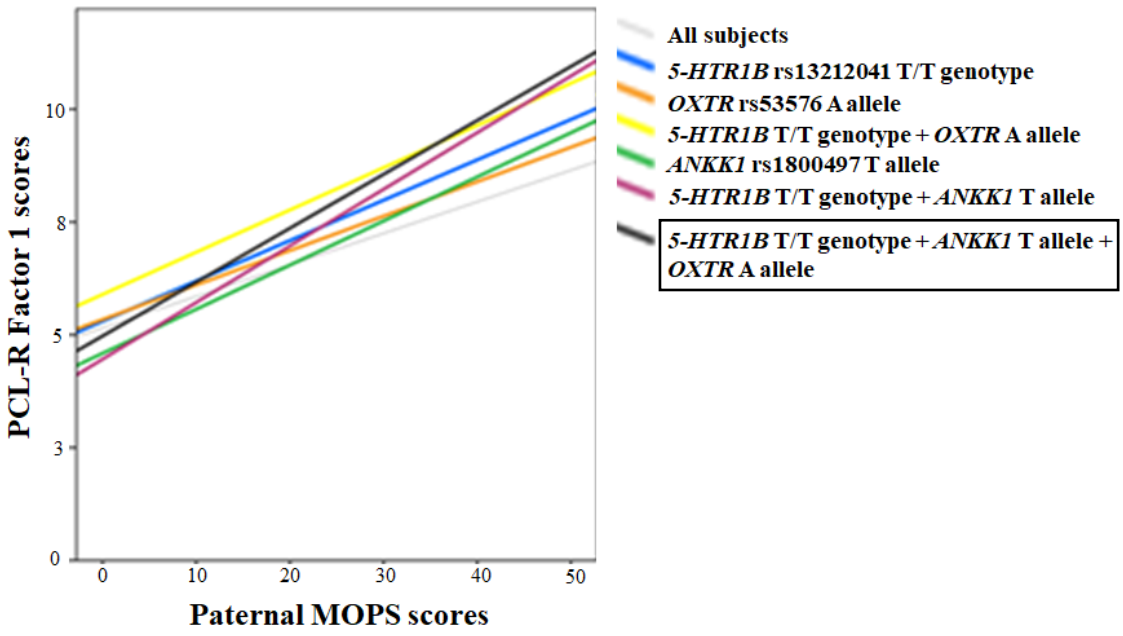

Figure 4.9. Correlations between Paternal MOPS scores and PCL-R Factor 1 scores for the *5-HTR1B* rs13212041 T/T genotype by *ANKK1* rs1800497 T allele by *OXTR* rs53576 A allele interaction. *5-HTR1B* rs13212041 T/T genotype + *ANKK1* rs1800497 T allele + *OXTR* rs53576 G/G genotype (β= 0.399, black line), as compared to any genotype (β= 0.214, grey line), *5-HTR1B* rs13212041 T/T genotype (β= 0.265, blue line), *ANKK1* rs1800497 T allele (β= 0.314, green line), *OXTR* rs53576 A allele (β= 0.241, orange line), *5-HTR1B* rs13212041 T/T genotype + ANKK1 rs1800497 T allele (β= 0.355, pink line), and *5-HTR1B* rs13212041 T/T genotype + *OXTR* rs53576 A allele (β= 0.296, yellow line). PCL-R= Psychopathy Checklist-revised, MOPS= Measure of Parental Style. PCL-R Factor 1= interpersonal/affective.

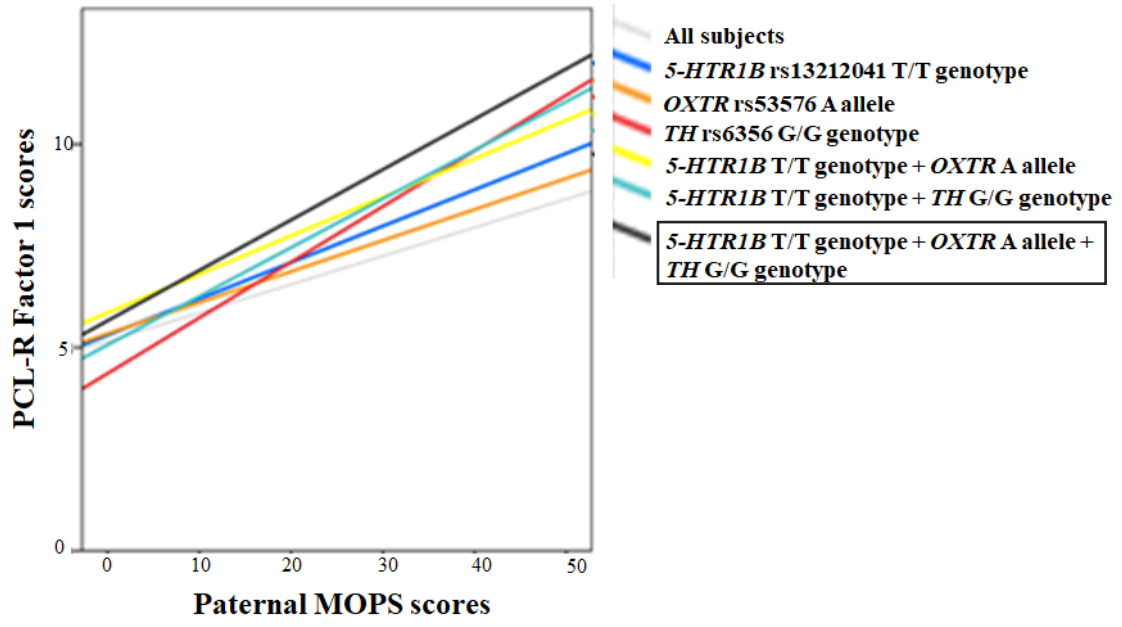

Figure 4.10. Correlations between Paternal MOPS scores and PCL-R Factor 1 scores for the *5-HTR1B* rs13212041 T/T genotype by *OXTR* rs53576 A allele by *TH* rs6356 G/G genotype interaction. *5-HTR1B* rs13212041 T/T genotype + *OXTR* rs53576 A allele + *TH* rs6356 G/G genotype (β= 0.425, black line) as compared to any genotype (β= 0.214, grey line), *5-HTR1B* rs13212041 T/T genotype (β= 0.265, blue line), *OXTR* rs53576 A allele (β= 0.241, orange line), *TH* rs6356 G/G genotype (β= 0.389, red line), *5-HTR1B* rs13212041 T/T genotype + *OXTR* rs53576 A allele (β= 0.296, green line), and *5-HTR1B* rs13212041 T/T genotype + *TH* rs6356 G/G genotype (β= 0.393, yellow line). PCL-R= Psychopathy Checklist-revised, MOPS= Measure of Parental Style. PCL-R Factor 1= interpersonal/affective.

Gene-by-gene interactions			Paternal MOPS by PCL-R Factor 1 correlations			
Combinations of genotypes			χ^2	df	p_{value}	$p_{Bonferroni\text{-}corrected}$
***5-HTR1B* rs13212041**		***ANKK1* rs1800497**				
T/T genotype	+	T allele	9.006	1	3×10^{-3}	**3.6×10^{-2}**
C allele	+	C/C genotype	0.100	1	0.752	1
T/T genotype	+	C/C genotype	3.784	1	0.054	0.648
C allele	+	T allele	3.884	1	4.9×10^{-2}	0.588
***5-HTR1B* rs13212041**		***TH* rs6356**				
T/T genotype	+	G/G genotype	11.722	1	1×10^{-3}	**1.2×10^{-2}**
C allele	+	A allele	1.058	1	0.304	1
C allele	+	G/G genotype	1.783	1	0.194	1
T/T genotype	+	A allele	3.794	1	0.053	0.636
***5-HTR1B* rs13212041**		***OXTR rs53576***				
T/T genotype	+	A allele	15.022	1	1×10^{-4}	**1.2×10^{-3}**
C allele	+	A allele	0.0002	1	0.999	1
C allele	+	G/G genotype	3.670	1	0.055	0.660
T/T genotype	+	G/G genotype	0.234	1	0.628	1
5-HTR1B rs13212041		*ANKK1* rs1800497	*TH* rs6356			
T/T genotype	+	T allele	+ G/G genotype	7.496	1	6×10^{-3}	0.144
C allele	+	C/C genotype	+ G/G genotype	0.0045	1	0.983	1
C allele	+	C/C genotype	+ A allele	0.201	1	0.654	1
C allele	+	T allele	+ G/G genotype	4.985	1	2.6×10^{-2}	0.624
C allele	+	T allele	+ A allele	1.955	1	0.162	1
T/T genotype	+	C/C genotype	+ G/G genotype	5.418	1	2×10^{-2}	0.48
T/T genotype	+	C/C genotype	+ A allele	0.989	1	0.320	1
T/T genotype	+	T allele	+ A allele	4.621	1	3.2×10^{-2}	0.768
5-HTR1B rs13212041		*TH* rs6356	*OXTR rs53576*			
T/T genotype	+	G/G genotype	+ A allele	11.718	1	1×10^{-3}	**2.4×10^{-2}**
C allele	+	G/G genotype	+ G/G genotype	0.063	1	0.802	1
C allele	+	G/G genotype	+ A allele	2.743	1	0.098	1
C allele	+	A allele	+ A allele	0.272	1	0.602	1
C allele	+	A allele	+ G/G genotype	2.819	1	0.093	1
T/T genotype	+	G/G genotype	+ G/G genotype	1.776	1	0.183	1
T/T genotype	+	A allele	+ A allele	6.971	1	8×10^{-3}	0.192
T/T genotype	+	G/G genotype	+ A allele	0.009	1	0.923	1
5-HTR1B rs13212041		*ANKK1* rs1800497	*OXTR rs53576*			
T/T genotype	+	T allele	+ A allele	13.431	1	3×10^{-4}	**7.2×10^{-3}**
C allele	+	C/C genotype	+ A allele	0.148	1	0.700	1
C allele	+	T allele	+ A allele	2.196	1	0.138	1
C allele	+	C/C genotype	+ G/G genotype	1.115	1	0.291	1
C allele	+	T allele	+ G/G genotype	3.553	1	0.059	1
T/T genotype	+	C/C genotype	+ A allele	6.502	1	1.1×10^{-2}	0.264
T/T genotype.	+	C/C genotype	+ G/G genotype	0.344	1	0.558	1
T/T genotype	+	T allele	+ G/G genotype	0.155	1	0.639	1

Table 4.14. Influence of the gene-by-gene interactions on the correlation between Paternal MOPS scores and PCL-R Factor 1 scores. Alpha level= 0.05/12 combinations of genotypes= 0.0042 for the interactions between two genetic variants. Alpha level= 0.05/24 combinations of genotypes = 0.002 for the interactions among three genetic variants. df= degrees of freedom. PCL-R= Psychopathy Checklist-revised, MOPS= Measure of Parental Style. PCL-R Factor 1= interpersonal/affective

c) PCL-R Lifestyle/Antisocial

A gene-by-gene interaction analysis was performed between the genetic variants (i.e., *5-HTR1B* rs13212041 and *OXTR* rs53576) that significantly influenced the correlation between Paternal MOPS scores and PCL-R Factor 2 scores (see **4.1.1.6**). This analysis did not produce any significant result (χ^2= 10.367, df= 4, p_{value}= 3.5×10^{-2}, $p_{Bonf.}$= 0.245).

4.1.2 Incarcerated adolescents

4.1.2.1 Distribution of psychometric, environmental, and demographic variables

The Shapiro-Wilk normality test indicated that the distribution of the demographic (age and IQ), and psychometric (PCL:YV) variables significantly deviated from the Gaussian distribution (**Table 4.15**).

Variables	Mean ± SD	Statistics	df	p_{value}
Age	17.02±1.12	0.805	180	$<10^{-6}$
IQ	92.05±12.96	0.973	171	2×10^{-3}
PCL:YV Total	23.478±6.125	0.983	169	3.8×10^{-2}
PCL:YV Factor 1	6.838±3.242	0.973	169	2×10^{-3}
PCL:YV Factor 2	14.364±3.276	0.947	169	6×10^{-6}

Table 4.15. Descriptive data and normality test for age, IQ, PCL:YV Total, PCL:YV Factor 1, and PCL:YV Factor 2 variables in the sample of incarcerated adolescents. PCL:YV= Psychopathy Checklist:Youth Version, SD= standard deviation, df= degrees of freedom. PCL:YV Factor 1= interpersonal/affective, PCL:YV Factor 2= lifestyle/antisocial.

Thirty (16.7%) of incarcerated adolescents scored 30 or higher at the PCL:YV questionnaire.

4.1.2.2 Search for collinearity between variables and confounding factors

The Spearman's rank-order correlation test indicated no significant collinearity between variables (**Table 4.16**).

The Spearman's rank-order correlation test indicated that age and IQ did not influence PCL:YV scores. The Mann–Whitney U test indicated that ethnicity did not influence PCL:YV scores (**Table 4.16**).

	Age	IQ	Ethnicity	PCL:YV Total	PCL:YV Factor 1	PCL:YV Factor 2
Age		ρ_s= 0.042 df= 171 p_{value}= 0.588	ρ_s= -0.101 df= 180 p_{value}= 0.175	ρ_s= -0.122 df= 169 p_{value}= 0.114	ρ_s= -0.116 df= 169 p_{value}= 0.134	ρ_s= -0.150 df= 169 p_{value}= 0.052
IQ	ρ_s= 0.042 df= 171 p_{value}= 0.588		ρ_s= 0.293 df= 171 p_{value}< 10^{-6}	ρ_s= -0.050 df= 165 p_{value}= 0.526	ρ_s= 0.042 df= 165 p_{value}= 0.589	ρ_s= -0.060 df= 165 p_{value}= 0.444
Ethnicity	ρ_s= -0.101 df= 180 p_{value}= 0.175	ρ_s= 0.293 df= 171 p_{value}< 10^{-6}		Z= -0.157 p_{value}= 0.875	Z= 1.887 p_{value}= 0.059	Z= -1.110 p_{value}= 0.267

PCL:YV Total	ρ_s= -0.122 df= 169 p_{value}= 0.114	ρ_s= -0.050 df= 165 p_{value}= 0.526	Z= -0.157 p_{value}= 0.875			
PCL:YV Factor 1	ρ_s= -0.116 df= 169 p_{value}= 0.134	ρ_s= 0.042 df= 165 p_{value}= 0.589	Z= 1.887 p_{value}= 0.059			ρ_s= 0.463 df= 169 p_{value}< **10^{-6}**
PCL:YV Factor 2	ρ_s= -0.150 df= 169 p_{value}= 0.052	ρ_s= -0.060 df= 165 p_{value}= 0.444	Z= -1.110 p_{value}= 0.267		ρ_s= 0.463 df= 169 p_{value}< **10^{-6}**	

Table 4.16. Search for collinearity between variables and confounding factors in the sample of incarcerated adults. Spearman's rank-order correlations (ρ_s) between PCL:YV Factor 1 and PCL:YV Factor 2 scores, and between age, IQ and ethnicity. Spearman's rank-order correlations between PCL:YV scores and age and between PCL:YV scores and IQ; Mann–Whitney U test (Z) to compare PCL:YV scores of Latin/Hispanics with those of not-Latin/Hispanics. PCL:YV= Psychopathy Checklist:Youth Version, IQ= Intelligence Quotient, df= degrees of freedom. PCL-R Factor 1= Interpersonal/Affective, PCL-R Factor 2= Lifestyle/Antisocial

4.1.2.3 Hardy-Weinberg equilibrium, Fisher's Exact Test and allele frequencies

The Chi-Square test showed that the allele and genotype frequencies were in Hardy-Weinberg equilibrium (**Table 4.17**).

In the whole sample, the frequencies of *TPH2* rs4570625 (p= 1.5×10^{-2}), *ANKK1* rs1800497 (p= 1.2×10^{-2}), and *COMT* rs4680 (p= 2.4×10^{-2}) genotypes gounpings were significantly different between Latin/Hispanics and not Latin/Hispanics (**Table 4.17**).

Pathways	Genetic variants	Genotype groupings	Genotypes	N	H-W eq	L/H	Not L/H	Fisher's Exact Test
Dopaminergic	*COMT* rs4680	A allele	A/A	33	χ^2= 0.329 p= 0.566	19	14	**p= 0.024**
			A/G	80		60	20	
		G/G	G/G	58		50	8	
	DRD4 exonIII VNTR	4/4	4/4	63	χ^2= 1.233 p= 0.267	47	16	p= 0.587
		not-4/4	2/4	15		9	6	
			3/4	7		3	4	
			4/5	1		1	0	
			4/6	7		7	0	
			4/7	51		43	8	
			4/8	2		1	1	
			2/2	2		1	1	
			2/7	4		1	3	
			5/7	2		2	0	
			7/7	16		14	2	
			7/8	1		1	0	
	DRD4 rs1800955	C allele	C/C	30	χ^2= 0.703 p= 0.402	19	11	p= 0.566
			T/C	90		69	21	
		T/T	T/T	52		41	11	

	SLC3A6 3'UTR VNTR	9R	9/10	68	χ^2= 2.726 p= 0.099	53	15	p= 0.593
			9/9	5		4	1	
			9/3	1		1	0	
			9/6	1		1	0	
			9/7	1		0	1	
		not-9R	10/10	100		74	26	
			10/3	1		1	0	
	ANKK1 rs1800497	T allele	T/T	23	χ^2= 0.485 p= 0.486	21	2	**p= 0.012**
			C/T	75		61	14	
		C/C	C/C	77		51	26	
	TH rs6356	A allele	A/A	30	χ^2= 0.870 p= 0.351	26	4	p= 0.289
			G/A	78		58	20	
		G/G	G/G	68		48	20	
Oxytocinergic	*OXTR* rs53576	A allele	A/A	16	χ^2= 1.474 p= 0.225	13	3	p= 0.475
			G/A	84		65	19	
		G/G	G/G	72		52	20	
	OXTR rs1042778	T allele	T/T	30	χ^2= 2.522 p= 0.217	24	6	p= 0.845
			G/T	92		68	24	
		G/G	G/G	48		35	13	
	OXTR rs237885	T allele	T/T	26	χ^2= 0.799 p= 0.371	18	8	p= 1
			T/G	88		67	21	
		G/G	G/G	56		42	14	
Serotonergic	*5-HTR1B* rs13212041	C allele	C/C	9	χ^2= 2.123 p= 0.145	4	5	p= 0.579
			T/C	49		38	11	
		T/T	T/T	121		93	28	
	MAOA uVNTR	High	4R	121	Not Applicable	88	33	p= 0.192
			3.5R	2		1	1	
		Low	3R	55		45	10	
			2R	1		1	0	
	5-HTTLPR	L/L	L_A/ L_A+ L_A /XL	46	χ^2= 0.140 p= 0.71	31	15	p= 0.166
		S allele	S/ L_A+ L_G/ L_A	87		63	24	
			S/S + S/ L_G	46		41	5	
	TPH2 rs4570625	T allele	T/T	18	χ^2= 1.207 p= 0.272	17	1	**p= 0.015**
			G/T	67		54	13	
		G/G	G/G	92		62	30	
	5-HTR2A rs6314	T allele	T/T	2	χ^2= 3.475 p= 0.062	2	0	p= 1
			C/T	17		13	4	
		C/C	C/C	159		119	40	

Table 4.17. Genotype groupings, genotypes, sample size (N), and Chi-square (χ^2) test to evaluate the Hardy-Weinberg equilibrium. Latin/Hispanic and not-Latin/Hispanic incarcerated adolescents were analyzed by the exact Fisher's test.
MOPS= Measure of Parental Style; L/H= Latin/Hispanics, not-L/H= not Latin/Hispanics, H-W eq= Hardy-Weinberg equilibrium.

The comparison of the allele frequencies observed in the sample of incarcerated adults with those reported by 1000 Genomes for the Europen-ancestry population showed remarkable differences in the frequencies of *COMT* rs4680 G allele, *ANKK1* rs1800497 T allele, and *TPH2* rs4570625 T allele observed in Latin/Hispanics (**Table 4.18**). Specifically, Latin-Hispanics exceded the allele frequencies reported by 1000 Genomes by 11%, 17%, and 12%, respectively. Moreover,

the *MAOA* uVNTR 4R allele, and 5-HTTLPR L allele observed in not-Latin/Hispanics exceded the allele frequencies reported by 1000 Genomes by 10%, and 11%, respectively (**Table 4.18**).

Polymorphisms	Allelic variants	Incarcerated adolescents			European ancestry
		Total	L/H	not-L/H	
COMT rs4680	G allele	0.57	0.62	0.43	0.51
	A allele	0.43	0.38	0.57	0.49
DRD4 exonIII VNTR	4R allele	0.61	0.61	0.62	0.64*
	7R allele	0.26	0.29	0.18	0.21*
DRD4 rs1800955	C allele	0.44	0.42	0.50	0.44
	T allele	0.56	0.58	0.50	0.56
DAT1 3'UTR VNTR	9R allele	0.23	0.24	0.21	0.27*
	10R allele	0.76	0.75	0.78	0.72*
ANKK1 rs1800497	C allele	0.65	0.61	0.79	0.82
	T allele	0.35	0.39	0.21	0.18
TH rs6356	G allele	0.61	0.58	0.68	0.60
	A allele	0.39	0.42	0.32	0.40
OXTR rs53576	G allele	0.66	0.65	0.70	0.66
	A allele	0.34	0.35	0.30	0.34
OXTR rs1042778	G allele	0.55	0.54	0.58	0.63
	T allele	0.45	0.46	0.42	0.37
OXTR rs237885	G allele	0.59	0.59	0.60	0.51
	T allele	0.41	0.41	0.40	0.49
5-HTR1B rs13212041	C allele	0.19	0.17	0.24	0.19
	T allele	0.81	0.83	0.76	0.81
TPH2 rs4570625	G allele	0.70	0.67	0.83	0.79
	T allele	0.30	0.33	0.17	0.21
5-HTR2A rs6314	C allele	0.94	0.94	0.95	0.92
	T allele	0.06	0.06	0.05	0.08
MAOA uVNTR	4R allele	0.68	0.65	0.75	0.65*
	3R allele	0.31	0.33	0.23	0.33*
5-HTTLPR	L allele	0.50	0.46	0.61	0.50*
	S allele	0.50	0.54	0.39	0.50*

Table 4.18. Allelic variants, allelic frequencies observed in Latin/Hispanic and not-Latin/Hispanic incarcerated adolescents, compared with expected allelic frequencies in European-anchestral population. L/H= Latin/Hispanics, not-L/H= not Latin/Hispanics. *allele frequencies obtained from literature data.

4.1.2.4 Associations between *5-HTR1B* rs13212041 and PCL:YV scores

The direct associations between *5-HTR1B* rs13212041 and psychopathy scores observed in the sample of incarcerated adults (**4.1.1.5**) was investigated in the replication sample of incarcerated adolescents.

Carriers of the *5-HTR1B* rs13212041 T/T genotype showed a mean PCL:YV Total score (24.48±6.16) significantly higher than C allele carriers (21.46±5.48) (χ^2= 10.372, df= 1, p_{value}= 10^{-3}, $p_{Bonf.}$= 10^{-3}; 1-β= 0.93, d= 0.52; **Figure 4.11a**). Linear regression showed that *5-HTR1B* rs13212041 T/T genotype produced a significant model that explained 4.8% of the variance of PCL:YV Total scores (R^2= 0.053, $F_{1,167}$= 9.368, $p_{Bonf.}$= $4\times10^{-3;}$ β= 0.231; $\beta_{Latin/Hispanics}$= 0.234, $p_{value} < 0.05$, N= 125; $\beta_{not\text{-}Latin/Hispanics}$= 0.221, $p_{value} > 0.05$, N= 43).

Moreover, the *5-HTR1B* rs13212041 T/T carriers scored higher than C allele carriers at PCL:YV Interpersonal/Affective (T/T: 7.34±3.28, C allele: 5.80±2.94; χ^2= 9.462, df= 1, p_{value}= 4×10^{-3}, $p_{Bonf.}$= 4×10^{-3}; 1-β= 0.91, d= 0.49; **Figure 4.11b**), but not at PCL:YV Lifestyle/Antisocial (χ^2 = 3.057, df = 1, p_{value}= 0.160, $p_{Bonf.}$= 0.160; 1-β= 0.53, d= 0.29). Linear regression showed that *5-HTR1B* rs13212041 T/T genotype produced a significant model that explained 4.4% of the variance of PCL:YV Anterpersonal/Affective scores (R^2= 0.049, $F_{1,167}$= 8.589, $p_{Bonf.}$= 8×10^{-3}; β= 0.222; $\beta_{Latin/Hispanics}$= 0.210, $p_{value} < 0.05$, N= 124; $\beta_{not\text{-}Latin/Hispanics}$= 0.290, $p_{value} > 0.05$, N= 42).

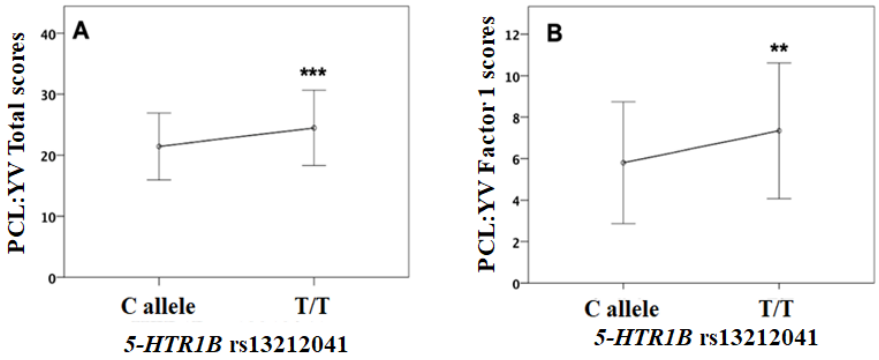

Figure 4.11.Associations between *5-HTR1B* rs13212041 and PCL:YV scores in incarcerated adults. A) PCL-R Total and B) PCL-R Factor 1. PCL:YV= Psychopathy Checklist:Youth Version.PCL:YV Factor 1= interpersonal/affective.

A priori power analyses suggested that in order to observe a significant difference in PCL:YV Total scores and PCL:YV Interpersonal/Affective scores, between *5-HTR1B* rs13212041 T/T genotype carriers and *5-HTR1B* rs13212041 C allele carriers, 124 and 140 are the minimum sample sizes required, respectively.

4.2. Youths with Conduct Disorder (CD)

4.2.1 Distribution of psychometric, environmental, and demographic variables

Shapiro-Wilk normality test indicated that the distribution of the demographic (age and IQ), psychometric (APSD Total and APSD-CU), and environmental (MI Total and MI Active) variables significantly deviated from the Gaussian distribution (**Table 4.19**).

Variables	Mean ± SD	Statistics	df	p_{value}
Age	9.46±1.756	0.889	119	$<10^{-6}$
IQ	99.81±8.668	0.969	117	9×10^{-3}
APSD Total	15.64±5.223	0.961	119	2×10^{-3}
APSD-CU	4.45±2.150	0.937	119	3×10^{-4}
MI Total	3.85±1.127	0.752	117	$<10^{-6}$
MI Active	2.69±0.905	0.745	117	$<10^{-6}$

Table 4.19. Descriptive data and normality test for age, IQ, APSD Total, APSD_CU, MI Total, and MI Active variables in the sample of youths with CD. IQ= Intellective Quotient, APSD= Antisocial Process Screening Device, CU= Callous-Unemotional, MI= Maltreatment Index, SD= standard deviation, df= degrees of freedom.

Thirty-nine (32.5%) of CD youths scored six or higher at the APSD-CU subscale.

Eighteen (15%), 52 (44%), and 19 (16%) of CD youths experienced neglect, emotional abuse, or physical abuse. Two (1.7%), ten (8.3%) and three (2.5%) of the youths experienced more severe (score of 3) neglect, emotional abuse, or physical abuse, respectively. None of the CD youths experienced sexual abuse.

4.2.2 Search for collinearity between variables and confounding factors

The Spearman's rank-order correlation test indicated no significant collinearity between variables (**Table 4.20**).

The Spearman's rank-order correlation test showed that age and IQ did not influence APSD Total and APSD-CU scores. The Mann–Whitney U test indicated ADHD as confounding factor for APSD Total scores (**Table 4.20**).

	Age	IQ	ADHD	APSD Total	APSD-CU
Age		ρ_s= -0.058 df= 117 p_{value}= 0.533	ρ_s= -0.093 df= 117 p_{value}= 0.318	ρ_s= 0.179 df= 117 p_{value}= 0.052	ρ_s= 0.110 df= 117 p_{value}= 0.235
IQ	ρ_s= 0.050 df= 916 p_{value}= 0.117		ρ_s= -0.001 df= 117 p_{value}= 0.991	ρ_s= -0.174 df= 117 p_{value}= 0.060	ρ_s= 0.020 df= 117 p_{value}= 0.829
ADHD	ρ_s= -0.093 df= 117 p_{value}= 0.318	ρ_s= -0.001 df= 117 p_{value}= 0.991		Z= 2.5 p_{value}= $1.2\times\mathbf{10^{-2}}$	Z= 0.869 p_{value}= 0.835
APSD Total	ρ_s= 0.179 df= 117 p_{value}= 0.052	ρ_s= -0.174 df= 117 p_{value}= 0.060	Z= 2.5 p_{value}= $1.2\times\mathbf{10^{-2}}$		
APSD-CU	ρ_s= 0.110 df= 117 p_{value}= 0.235	ρ_s= 0.020 df= 117 p_{value}= 0.829	Z= 0.869 p_{value}= 0.835		

Table 4.20. **Search for confounding factors in the sample of youths with CD.** Spearman's rank-order correlations (ρ_s) between between age, IQ and ADHD. Spearman's rank-order correlation between APSD scores and age and between APSD scores and IQ; Mann–Whitney U test (Z) test to compare APSD scores of children with ADHD with those of children without ADHD. ADHD= Attention Deficit Hyperactivity Disorder, IQ= Intelligence quotient, APSD= Antisocial Process Screening Device, CU= Callous-Unemotional, df= degrees of freedom.

4.2.3 Hardy-Weinberg equilibrium and allele frequencies

The Chi-square test showed that the allele and genotype frequencies were in Hardy-Weinberg equilibrium (**Table 4.21**).

Pathways	Genetic variants	Genotype groupings	Genotypes	N	H-W eq
Dopaminergic	*ANKK1* rs1800497	T allele	T/T	2	χ^2= 0.616 p= 0.433
			C/T	35	
		C/C	C/C	83	
	TH rs6356	A allele	A/A	32	χ^2= 0.411 p= 0.522
			G/A	56	
		G/G	G/G	31	
	COMT rs4680	A allele	A/A	17	χ^2= 0.809 p= 0.368
			A/G	62	
		G/G	G/G	40	
	DRD4 exonIII VNTR	4/4	4/4	58	χ^2= 2.307 p= 0.129
		not-4/4	4/5	4	
			4/7	24	
			4/8	2	
			7/7	6	
			2/4	14	

			2/5	1	
			2/6	1	
			2/7	4	
			3/4	5	
	DRD4 rs1800955	G allele	G/G	32	χ^2= 1.195 p= 0.274
			T/G	65	
		T/T	T/T	22	
	SLC6A3 3'UTR VNTR	9R	9/9	10	χ^2= 1.065 p= 0.302
			10/9	56	
			11/9	2	
		not-9R	10/10	50	
			10/11	1	
Oxytocinergic	*OXTR* rs53576	A allele	A/A	9	χ^2= 0.103 p= 0.748
			G/A	50	
		G/G	G/G	60	
	OXTR rs1042778	T allele	T/T	14	χ^2= 1.069 p= 0.645
			G/T	61	
		G/G	G/G	44	
	OXTR rs237885	T allele	T/T	31	χ^2= 0.832 p= 0.362
			T/G	55	
		G/G	G/G	33	
Serotonergic	*5-HTR1B* rs13212041	C allele	C/C	3	χ^2= 0.630 p= 0.427
			T/C	25	
		T/T	T/T	91	
	MAOA uVNTR	High	3.5	3	Not applicable
			4	86	
		Low	2	1	
			3	29	
	5-HTTLPR	L/L	L_A/ L_A	42	χ^2= 0.359 p= 0.549
		S allele	S/ L_A+ L_G/ L_A	60	
			S/S + S/ L_G	17	
	TPH2 rs4570625	T allele	T/T	6	χ^2= 0.003 p= 0.958
			G/T	41	
		G/G	G/G	72	
	5-HTR2A rs6314	T allele	T/T	1	χ^2= 0.235 p= 0.628
			C/T	25	
		C/C	C/C	93	

Table 4.21. Genotype groupings, genotypes, sample size (N), and Chi-square (χ^2) test to evaluate the Hardy-Weinberg equilibrium in the sample of youths with CD. H-W eq= Hardy-Weinberg equilibrium

The comparison of the allele frequencies observed in the sample of incarcerated adults with those reported by 1000 Genomes for the Europen-ancestry population showed remarkable differences in the frequencies of *DRD4* rs1800955 C allele, *TH* rs6356 A allele, and 5-HTTLPR L allele observed in CD youths (**Table 4.22**). Specifically, CD youths exceded the allele frequencies reported by 1000 Genomes by 10%, for all the three allelic variants.

Polymorphisms	Allelic variants	CD youths	European ancestry
COMT rs4680	G allele	0.59	0.51
	A allele	0.41	0.49

DRD4 exonIII VNTR	4R allele	0.68	0.64*
	7R allele	0.17	0.21*
DRD4 rs1800955	C allele	0.54	0.44
	T allele	0.46	0.56
DAT1 3'UTR VNTR	9R allele	0.33	0.27*
	10R allele	0.66	0.72*
ANKK1 rs1800497	C allele	0.84	0.82
	T allele	0.16	0.18
TH rs6356	G allele	0.50	0.60
	A allele	0.50	0.40
OXTR rs53576	G allele	0.73	0.66
	A allele	0.27	0.34
OXTR rs1042778	G allele	0.63	0.63
	T allele	0.37	0.37
OXTR rs237885	G allele	0.51	0.51
	T allele	0.49	0.49
5-HTR1B rs13212041	C allele	0.13	0.19
	T allele	0.87	0.81
TPH2 rs4570625	G allele	0.78	0.79
	T allele	0.22	0.21
5-HTR2A rs6314	C allele	0.89	0.92
	T allele	0.11	0.08
MAOA uVNTR	4R allele	0.72	0.65*
	3R allele	0.24	0.33*
5-HTTLPR	L allele	0.60	0.50*
	S allele	0.40	0.50*

Table 4.22. Allelic variants, allelic frequencies observed in CD youths compared with expected allelic frequencies in European-anchestral population. *allele frequencies obtained from literature data.

4.2.4 Associations between MI scores and APSD scores

Mean APSD scores were not significantly different between maltreated youths and non-maltreated youths (APSD Total*MI Total: χ^2= 0.839, df= 1, p_{value}= 0.360; APSD Total*MI Active: χ^2= 1.392, df= 1, p_{value}= 0.238; APDS-CU*MI Total: χ^2= 0.242, df= 1, p_{value}= 0.622; APDS-CU*MI Active: χ^2= 0.111, df= 1, p_{value}= 0.739).

4.2.5 Associations between *5-HTR1B* rs13212041 and APSD scores

The direct association between *5-HTR1B* rs13212041 and psychopathy scores observed in the sample of incarcerated adults (see **4.1.1.5**) and replicated in the sample of incarcerated adolescents (see **4.1.2.4**) was investigated in youths with CD.

5-HTR1B rs13212041 was not significantly associated with APSD scores (APSD Total: χ^2= 0.269, df= 1, p_{value}= 0.604; APSD-CU: χ^2= 0.059, df= 1, p_{value}= 0.809).

4.2.6 Genetic variants by MI by APSD interactions

The significant influences of *5-HTR1B* rs13212041, *ANKK1* rs1800497, *TH* rs6356, and *OXTR* rs53576 on the correlation between maltreatment and psychopathy scores observed in the sample of incarcerated adults (see **4.1.1.6**) were investigated in youths with CD.

A significant interaction among *ANKK1* rs1800497, MI Active, and APSD-CU scores (χ^2= 8.972, df= 2, p= 1.2×10^{-2}, $p_{Bonf.}$= 4.8×10^{-2}) was observed. Specifically, among youths with active maltreatment, carriers of the *ANKK1* rs1800497 T allele showed a mean APSD-CU score (5.65±2.52) significantly higher than C/C genotype carriers (3.75±2.01) (p= 3×10^{-3}, $p_{Bonf.}$= 6×10^{-3}; **Figure 4.12**).

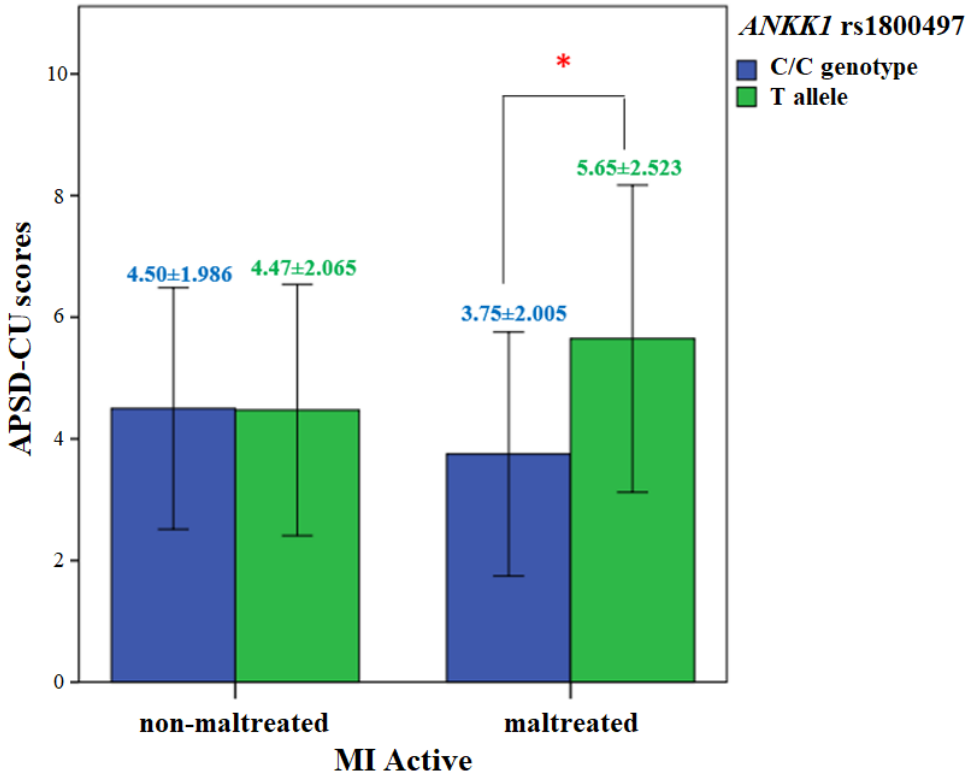

Figure 4.12. Mean APSD-CU scores in the presence or absence of active maltreatment divided by *ANKK1* rs1800497 genotype groupings in youths with CD. APSD= Antisocial Process Screening Device, CU= Callous-Unemotional, MI= Maltreatment Index.

In youths without active maltreatment, APSD-CU mean scores were not different between *ANKK1* rs1800497 T allele carriers (4.47±2.07) and *ANKK1* rs1800497 C/C genotype carriers (4.50±1.99) (p_{value}= 0.962, $p_{Bonf.}$= 1) (**Figure 4.12**).

ANKK1 rs1800497 did not significantly influence the associations between APSD-CU scores and MI Total scores or between APSD Total scores and MI scores (Total and Active) (**Table 4.23**).

5-HTR1B rs13212041, *TH* rs6356, and *OXTR* rs53576 did not significantly influence the associations between MI scores (Total and Active) and APSD scores (Total and CU) (**Table 4.23**).

Interactions among genotypes, MI Active, and APSD-CU scores				
Polymorphisms	**χ^2**	**df**	**p_{value}**	**$p_{Bonferroni\text{-}corrected}$**
5-HTR1B rs13212041	2.049	2	0.359	1
TH rs6356	0.032	2	0.984	1
OXTR rs53576	4.080	2	0.130	0.520
Interactions among genotypes, MI Total, and APSD-CU scores				
Polymorphisms	**χ^2**	**df**	**p_{value}**	**$p_{Bonferroni\text{-}corrected}$**
5-HTR1B rs13212041	2.281	2	0.320	1
ANKK1 rs1800497	6.074	2	0.048	0.176
TH rs6356	0.188	2	0.910	1
OXTR rs53576	3.980	2	0.137	0.548
Interactions among genotypes, MI Active, and APSD Total scores				
Polymorphisms	**χ^2**	**df**	**p_{value}**	**$p_{Bonferroni\text{-}corrected}$**
5-HTR1B rs13212041	2.789	2	0.248	0.992
ANKK1 rs1800497	5.013	2	0.082	0.328
TH rs6356	1.001	2	0.606	1
OXTR rs53576	0.706	2	0.702	1
Interactions among genotypes, MI Total, and APSD Total scores				
Polymorphisms	**χ^2**	**df**	**p_{value}**	**$p_{Bonferroni\text{-}corrected}$**
5-HTR1B rs13212041	3.203	2	0.202	0.808
ANKK1 rs1800497	4.152	2	0.125	0.500
TH rs6356	1.036	2	0.596	1
OXTR rs53576	1.152	2	0.562	1

Table 4.23. Interactions among genotypes, MI, and APSD scores. Alpha level= 0.05/4 genetic variants= 0.0125. MI= Maltreatment Index, APSD= Antisocial Process Screening Device, CU= Callous-Unemotional, df= degrees of freedom.

4.2.7 Effect of gene-by-gene interactions on the association between Active Maltreatment and ASPD-CU scores

The significant interaction observed among *ANKK1* rs1800497, MI Active, and APSD-CU scores in youths with CD (see **4.2.6.**) was further analyzed in interaction with *5-HTR1B* rs13212041, *OXTR* rs53576, and *TH* rs6356, as suggested by the gene-by-gene interaction results observed in the sample of incarcerated adults (see **4.1.1.8**).

Because of the small size of the sample of youths with CD, carriers of both *ANKK1* rs1800497 T allele and *5-HTR1B* rs13212041 T/T genotype, or *ANKK1* rs1800497 T allele and *OXTR* rs53576 A allele, or *ANKK1* rs1800497 T allele and *TH* rs6356 G/G genotype, were compared to all the remaining subjects (subjects with only one or no risk alleles). This strategy drastically reduced the degrees of freedom of the statistical analysis.

A significant interaction among the *ANKK1* rs1800497 by *5-HTR1B* rs13212041 interaction, MI Active, and APSD-CU scores (χ^2= 12.505, df= 2, p_{value}= 2×10^{-3}, $p_{Bonf.}$= 6×10^{-3}) was observed. Specifically, among youths with active maltreatment, carriers of both *ANKK1* rs1800497 T allele and *5-HTR1B* rs13212041 T/T genotype showed a mean APSD-CU score (6.17±2.37, APSD-CU

cut-off= 6) significantly higher than youths without these genotypes (3.83±2.07) (p_{value}= 4×10^{-3}, $p_{Bonf.}$= 2.4×10^{-2}; **Figure 4.13**).

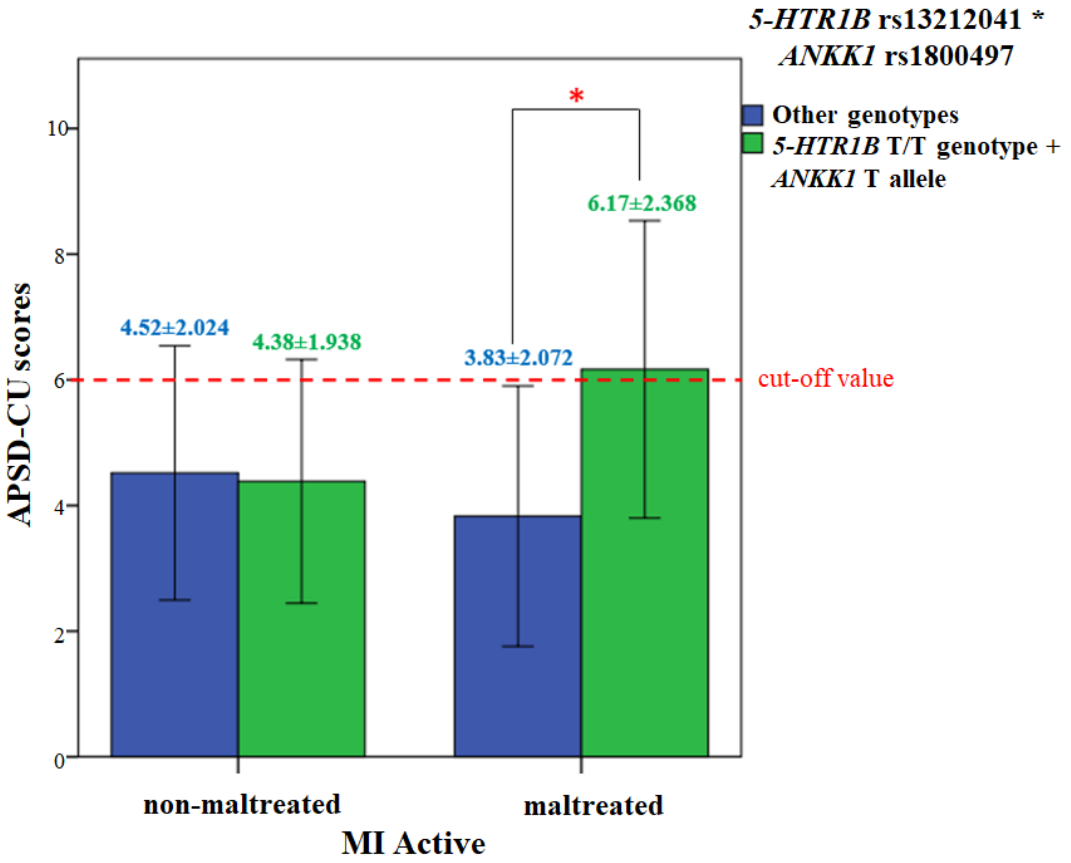

Figure 4.13. Mean APSD-CU scores in the presence or absence of active maltreatment in youths with CD with or without both *5-HTR1B* rs13212041 T/T genotype and *ANKK1* rs1800497 T allele. APSD= Antisocial Process Screening Device, CU= Callous-Unemotional, MI= Maltreatment Index.

In youths without active maltreatment, APSD-CU scores were not significantly different between carriers of both *ANKK1* rs1800497 T allele and *5-HTR1B* rs13212041 T/T genotype (4.38±1.94) and youths without these genotypes (4.52±2.02) (p_{value}= 0.820, $p_{Bonf.}$= 1) (**Figure 4.13**).

The gene-by-gene interaction between *ANKK1* rs1800497 and *OXTR* rs53576 was not significantly associated with MI Active and APSD-CU scores (χ^2= 7.953, df= 2, p_{value}= 1.9×10^{-2}, $p_{Bonf.}$= 0.076). The gene-by-gene interaction between *ANKK1* rs1800497 and *TH* rs6356 was not performed due to the low number of subjects with both *ANKK1* rs1800497 T allele and *TH* rs6356 G/G genotype (N= 4).

4.3 Summary of significant results

	Incarcerated adults	Incarcerated adolescents	Youths with CD
***5-HTR1B* rs13212041 T/T genotype * psychopathy**	**PCL-R Total** $p_{Bonf.}= 1.5\times10^{-2}$ / Variance= 1.2%	**PCL:YV Total** $p_{Bonf.}= 1\times10^{-3}$ / Variance= 4.8%	APSD Total Not associated
	PCL-R Factor 1 $p_{Bonf.}= 6\times10^{-3}$ / Variance= 0.5%	**PCL:YV Factor 1** $p_{Bonf.}= 8\times10^{-3}$ / Variance= 4.4%	APSD-CU Not associated
	PCL-R Factor 2 $p_{Bonf.}= 2\times10^{-3}$ / Variance= 1.4%	PCL:YV Factor 2 Not associated	-
	Interaction with Paternal MOPS	**Environmental data not available**	**Interaction with MI**
Psychopathy * maltreatment	**PCL-R Total** $p_{Bonf.}= 6\times10^{-3}$ / Variance= 4.6%	-	APSD Total * MI Active Not associated
	PCL-R Factor 1 $p_{Bonf.}= 2.2\times10^{-2}$ / Variance= 4.1%	-	APSD-CU*MI Active Not associated
	PCL-R Factor 2 $p_{Bonf.}= 2.4\times10^{-2}$ / Variance= 1.7%	-	-
	Interaction with Paternal MOPS	**Environmental data not available**	**Interaction with MI**
***5-HTR1B* rs13212041 T/T genotype * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 2.8\times10^{-2}$ / Variance= 7.4%	-	APSD Total * MI Active Not associated
	PCL-R Factor 1 $p_{Bonf.}= 1.4\times10^{-2}$ / Variance= 6.4%	-	APSD-CU*MI Active Not associated
	PCL-R Factor 2 $p_{Bonf.}= 1.4\times10^{-2}$ / Variance= 4%	-	-
***ANKK1* rs1800497 T allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 2.8\times10^{-2}$ / Variance= 10%	-	APSD Total * MI Active Not associated
	PCL-R Factor 1 $p_{Bonf.}= 6\times10^{-3}$ / Variance= 9%	-	**APSD-CU*MI Active** $p_{Bonf.}= 6\times10^{-3}$
***TH* rs6356 G/G genotype * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 2.8\times10^{-2}$ / Variance= 13.9%	-	APSD Total * MI Active Not associated
	PCL-R Factor 1 $p_{Bonf.}= 2.8\times10^{-4}$/ Variance= 13.7%	-	APSD-CU*MI Active Not associated
***OXTR* rs53576 A allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 4.9\times10^{-2}$ / Variance= 7.3	-	APSD Total * MI Active Not associated
	PCL-R Factor 1 $p_{Bonf.}= 4\times10^{-3}$/ Variance= 5%	-	APSD-CU*MI Active Not associated
	PCL-R Factor 2 $p_{Bonf.}= 4\times10^{-3}$ / Variance= 5.3%	-	-
***5-HTR1B* rs13212041 T/T genotype * *ANKK1* rs1800497 T allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 2.3\times10^{-3}$ / Variance= 16.2%	-	APSD-CU*MI Active Not associated
	PCL-R Factor 1 $p_{Bonf.}= 3.6\times10^{-2}$/ Variance= 11.5%	-	**APSD-CU*MI Active** $p_{Bonf.}= 2.4\times10^{-2}$
***5-HTR1B* rs1321204 T/T genotype * *OXTR* rs53576 A allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 2.3\times10^{-3}$ / Variance= 16.2%	-	-
	PCL-R Factor 1 $p_{Bonf.}= 1.2\times10^{-3}$ / Variance= 7.7%	-	-
***5-HTR1B* rs13212041 T/T genotype * *TH* rs6536 T allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 2.4\times10^{-2}$ / Variance= 15.3%	-	-
	PCL-R Factor 1 $p_{Bonf.}= 1.2\times10^{-2}$ / Variance= 13.4%	-	-
***ANKK1* rs1800497 T allele* *OXTR* rs53576A allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 1.2\times10^{-2}$ / Variance= 16.1%	-	APSD-CU*MI Active Not associated
***ANKK1* rs1800497 T allele* *TH* rs6356 G/G genotype * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 1.7\times10^{-4}$ / Variance= 35.4%	-	-
***TH* rs6356 G/G genotype* *OXTR* rs53576 A allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 1.4\times10^{-3}$ / Variance= 22.1%	-	-
***5-HTR1B* rs13212041 T/T genotype * *ANKK1* rs1800497 T allele * *TH* rs6356 G/G genotype * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}<10^{-6}$ / Variance= 43%	-	-
***5-HTR1B* rs13212041 T/T genotype * *ANKK1* rs1800497 T allele * *OXTR* rs53576 A allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}<10^{-6}$ / Variance= 18%	-	-
	PCL-R Factor 1 $p_{Bonf}= 7.2\times10^{-3}$ / Variance= 14.1%		-
***5-HTR1B* rs13212041 T/T genotype * *TH* rs6356 G/G genotype * *OXTR* rs53576 A allele * psychopathy * maltreatment**	**PCL-R Total** $p_{Bonf.}= 1.2\times10^{-6}$ / Variance= 39%	-	-
	PCL-R Factor 1 $p_{Bonf}= 2.4\times10^{-2}$ / Variance= 14.5%	-	-

Chapter 5

Discussion, limitations, and conclusions

5.1 Discussion

Within the framework of a wider project in collaboration with the University of New Mexico and the IRCCS Stella Maris Foundation (Pisa), my Ph.D. work focused on the investigation of genetic and environmental correlates of psychopathic traits, from childhood to adulthood, with the aim of identifying early genetic predictors of psychopathy that might improve the rate of success in preventing youths with Conduct Disorder (CD) to develop psychopathy. Youths with early-onset CD, indeed, are known to be at risk of developing life-course-persistent antisocial problems (Odgers et al., 2008).

Specifically, 14 polymorphisms belonging to the serotonergic, dopaminergic and oxytocinergic pathways were genotyped in three groups of subjects with severe antisocial behavior, representative of three different age of life: a large group of incarcerated adults, a smaller group of incarcerated adolescent and a group of children with Conduct Disorder (see Materials and Methods for more details).

The obtained results showed that childhood maltreatment (assessed by MOPS) was associated with psychopathy (measured by PCL-R) in the incarcerated adults. Moreover, the *5-HTR1B* rs13212041 T/T genotype increased the risk of psychopathy in both the incarcerated adults and adolescents (in whom psychopathy was assessed by PCL-YV). In addition, the gene by environment interaction analysis showed that specific genotypes of *5-HTR1B* rs13212041, *ANKK1* rs1800497, *TH* rs6356, and *OXTR* rs53576, as well as their different combinations increased the correlation between psychopathy scores and childhood maltreatment in incarcerated adults. Finally, in children exposed to active maltreatment (assessed by MI) the *ANKK1* rs1800497 T allele, both per se and in interaction with the *5-HTR1B* rs13212041 T/T genotype, was associated with CU traits (measured by APSD-CU subscale), which are personality characteristics predictive of life-long affective psychopathy (for a review see Frick et al., 2014_b). Our findings indicated these two genetic variants as potential early biomarkers of psychopathy.

In details, in the sample of incarcerated adults, paternal indifference, overcontrol, and abuse measured by MOPS, significantly correlated with psychopathy scores, explaining 4.6% of the variance of PCL-R Total scores, 4.1% of the variance of PCL-R Factor 1 scores, and 1.7% of the variance of PCL-R Factor 2 scores, suggesting that paternal maltreatment predispose more to interpersonal/affective problems than to antisocial lifestyle.

These results are in line with previously published evidence showing that paternal indifference is a risk factor for the interpersonal/affective dimension of psychopathy (Gao et al., 2010).

Moreover, childhood aversive experiences, such as emotional (Schimmenti et al., 2015), physical (Kolla et al., 2013) and sexual (Graham et al., 2012; Boduszek et al., 2019) abuses, have been associated with psychopathic traits (Campbell et al., 2004; Hunter et al., 2010; Krischer & Sevecke, 2008; O'Neill et al., 2003). Finally, other studies suggested that being physically or emotionally neglected by parents plays an important role in the development of psychopathy (Cima et al., 2008; Craparo et al., 2013; Dargis & Koenigs, 2018; Weiler & Widom, 1996; Graham et al., 2012; Koivisto et al., 1996) and psychopathic traits (O'Neill et al., 2003; Ometto et al., 2016; Schraft et al., 2013; Weiler & Widom, 1996).

Thus, the scientific literature suggests that both paternal and maternal maltreatment affect psychopathic traits (Kimbrel et al., 2007; Gao et al., 2010); in our sample of incarcerated adults, maternal maltreatment was not significantly associated with psychopathy scores. We observed that Maternal MOPS scores were much lower than Paternal MOPS scores, suggesting that these subjects were not exposed to particularly severe episodes of maternal maltreatment during childhood. Of note, higher sensitivity to paternal maltreatment and likelyhood to be abused from fathers has been observed in boys as compared to girls (Cui et al., 2016; Godbout et al., 2019).

Also the MI questionnaire, used for youths with CD, investigated neglect, emotional abuse, and physical abuse, but it wasadministered to only one parent, either the father or the mother, thus preventing us from separating paternal from maternal maltreatment. In our sample of CD youths, we observed that maltreatment did not significantly influence APSD Total scores or APSD-CU scores, in line with previous findings by our collaborators (Milone et al., 2019).

Other authors, instead, have shown that severe maltreatments, mostly physical (Portnoy et al., 2020) and sexual abuse (Cecil et al., 2018), are risk factors for higher APSD Total and APSD-CU scores (for review see Joyner and Beaver, 2021). In children removed from caregiver, for example, APSD scores have been associated with severe abuse (physical, sexual, and emotional) and neglect (Metcalf et al., 2021). Furthermore, in substantiated cases of severe childhood physical abuse, sexual abuse, and neglect, processed in the county juvenile or adult criminal courts,

maltreatment has been associated with CU traits (Widom et al., 2020). However, it is worthy to note that, in our sample, among the 44% CD youths that experienced emotional abuse only the 8.3% suffered severe (score > 3) emotional abuse, as well as among the 16% that experienced physical abuse only the 2.5% suffered severe (score > 3) physical abuse. Furthermore, none of them experienced sexual abuse. Overall, our cohort of children was characterized by a history of mild emotional abuse with rare episodes of severe physical abuse. Moreover, the role of maltreatment in CU traits is still controversial and far from being completely elucidated. Harsh parenting and parental maltreatment, indeed, can be also elicited by CU traits (Milone et al., 2019) suggesting a complex interplay between CU traits and negative parenting (Milone et al., 2019).

Concerning the genetic association analysis, we observed that the *5-HTR1B* rs13212041 T/T genotype, as compared to the *5-HTR1B* rs13212041 C allele, was associated with higher PCL-R and PCL:YV scores in incarcerated adults and adolescents, respectively. In particular, the *5-HTR1B* rs13212041 T/T genotype affected both the Interpersonal/Affective and the Lifestyle/Antisocial dimensions of PCL-R, but only the Interpersonal/Affective dimension of PCL:YV.

The *5-HTR1B* gene encodes for the 5-HT receptor 1B that is mostly expressed on the pre-synaptic terminals of serotonergic neurons, where it regulates neuronal firing through a negative feedback signal; the interaction between serotonin (5-HT) and pre-synaptic 5-HTR1Bs inhibits further release of 5-HT in the synaptic cleft (Nichols & Nichols, 2008). The *5-HTR1B* rs13212041 T allele favors the binding of a miRNA to the mRNA 3' untranslated region (UTR) of *5-HTR1B*, which reduces its expression (Jensen et al., 2009; Jensen et al., 2011). In line with our findings, the *5-HTR1B* rs13212041 T/T genotype has been previously found associated with anger and hostility (Jensen et al., 2009; Conner et al., 2010), as well as low 5-HTR1B levels have been associated with aggressive and impulsive behavior (Nautiyal et al., 2015; Zhuang et al., 1999; Sadou 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), which are all key components of psychopathy.

Of note, the genetic association in adolescents was observed even if the sample size was five times smaller as compared to the sample of adults. Moreover, the variances, explained by the *5-HTR1B* rs13212041 T/T genotype, of PCL:YV Total scores (4.8%) and PCL:YV Interpersonal/Affective scores (4.4%) were four times and nine times greater than the variances of PCL-R Total scores (1.2%) and PCL-R Interpersonal/Affective scores (0.5%), respectively. These results indicated that the effect of the *5-HTR1B* rs13212041 T/T genotype on psychopathy was stronger in youths than in adults.

Starting from the effect sizes observed in incarcerated adults, an a priori power analysis suggested 518 and 896 as the minimum sample sizes to appreciate significant associations with total psychopathy scores and interpersonal/affective scores, respectively. The sample of incarcerated adolescent included only 180 subjects. I decided to test anyway the possible influence of *5-HTR1B* rs13212041 on PCL:YV scores, because genetics has been hypothesized to show a stronger effect at younger ages (Hyde et al., 2016; Waller et al., 2016). Genetic factors, indeed, "*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*"-Palumbo et al., 2022_a. According to this hypothesis, novel gene-by-gene and gene-by-environment interactions during aging (Takahashi et al., 2021) may mitigate previous effects of other genes (Hyde et al., 2016; Waller et al., 2016). This phenomenon, known as "genetic innovation", is thought to be a consequence of hormonal, neuroanatomical, and neurochemical changes involved in brain maturation (Spear, 2000; Takahashi et al., 2021). My decision turned out to be correct, as the effect sizes of *5-HTR1B* rs13212041 T/T genotype on psychopathy in incarcerated adolescents (PCL:YV Total:d= 0.52; PCL:YV Interpersonal/Affective: d= 0.49) were more than doubled as compared to the effect sizes observed in adult offenders (PCL-R Total: d= 0.25; PCL-R Interpersonal/Affective 1: d= 0.19), thus allowing me to detect the associations despite the small sample size.

However, the association of *5-HTR1B* rs13212041 T/T genotype with only PCL:YV Factor 1, but not with PCL:YV Factor 2 in adolescents, suggested that, at younger ages, the T/T genotype has a greater impact on the interpersonal/affective deficits than on the antisocial lifestyle. This hypothesis is corroborated by previous evidence showing that increased serotonergic signaling correlates with higher PCL-SV (*Psychopathy Checklist-Screening Version*) Interpersonal/Affective scores (Dolan & Anderson, 2003) and lower levels of guilt (Kanen et al., 2021) that is a core feature of the interpersonal/affective dimension of psychopathy (Hare, 2003). In line with a potential role of the *5-HTR1B* rs13212041 T/T genotype on affective deficits, the 5-*HTR1B* promoter methylation, an epigenetic mechanism that decreases gene expression, has been previously found associated with CU traits in youths (Moul et al., 2015).

Considering the effect sizes observed in the sample of adolescents, an a priori power analysis suggested 124 and 140 as minimum sample sizes to appreciate the above reported significant associations. The sample of youths with CD comprised 120 subjects, but contrary to the genetic innovation theory, this sample size was not large enough to appreciate a significant direct effect of *5-HTR1B* rs13212041 neither on APSD Total scores nor on APSD-CU scores. A possible explanation could be that the APSD, which is a parent-report questionnaire, is not perfectly

equivalent to both PCL-R and PCL:YV that are clinician-report questionnaires. Indeed, several items of PCL-R or PCL:YV (e.g., parasitic lifestyle, early behavioral problems, conditional release, criminal versatility, and promiscuous sexual behavior) are not included in the APSD questionnaire (Lee, Vincent, Hart, & Corrado, 2003; Frick & Dickens 2006), as they do not apply to children.

Regarding the gene by environment by psychopathy interaction analysis, we observed a significant interaction between *5-HTR1B* rs13212041 and Paternal MOPS scores. In particular, the *5-HTR1B* rs13212041 T/T genotype significantly increased the variances explained by Paternal MOPS scores of PCL-R Total scores (up to 7.4%), PCL-R Interpersonal/Affective scores (up to 6.4%), and PCL-R Lifestyle/Antisocial scores (up to 4%). Nevertheless, the moderation analysis confirmered that the the *5-HTR1B* rs13212041 T/T genotype significantly moderated the effect of Paternal MOPS scores on PCL-R Total scores, PCL-R Interpersonal/Affective scores and PCL-R Lifestyle/Antisocial scores. In line with this observation, social isolation in mice (Bibancos et al., 2007) and severe trauma exposure in humans (Murrough et al., 2011) have been shown to reduce the availability of 5-HTR1B in several brain regions, including the amygdala.

We hypothesized that the *5-HTR1B* rs13212041 T/T genotype and paternal maltreatment may synergistically act to decrease the expression of *5-HTR1B,* thus increasing the brain availability of 5-HT. A greater 5-HT availability has been shown to decrease the amygdala reactivity in response to fearful facial expressions (Murphy et al., 2009), and low amygdala reactivity to emotional stimuli is typical of both adult with psychopathy (Birbaumer et al., 2005; Dolan et al., 2009; Kiehl et al., 2001; Rilling et al., 2007; Deeley et al., 2006; Gordon & End, 2004) and CU-children (Marsh et al., 2008; Jones et al., 2009). This deficit has been observed during different experimental paradigms, including the stimulus-reinforcement learning, aversive conditioning, fear-potentiated startle, passive avoidance learning, and fearful facial expression recognition (Blair et al., 2006). In addition, an altered reactivity to emotional stimulihas been observedin individuals with amygdala lesions (Blair et al., 2006; Patrick, 2006); our findings further supports a key role for amygdala dysfunctions in bothCU traits and psychopathy.

Overall, the obtained results suggest that the *5-HTR1B* rs13212041 T/T genotype might represent a risk factor for both psychopathic dimensions, albeit to a different extent. Of note, the 5-HTR1B is also a post-synaptic auto-receptor on serotonergic neurons and a hetero-receptor on dopaminergic, glutamatergic, GABAergic, and acetyl-cholinergic neurons (Nichols & Nichols, 2008). Due to the dual activity of 5-HTR1B, both as pre-synaptic auto-receptor and as post-synaptic auto- or hetero-receptor, 5-HTR1Bs with different localizations and functions may differentially affect the two dimensions of psychopathy.

As far as the dopaminergic pathway is concerned, the *ANKK1* rs1800497 T allele significantlyincreased the variances explained by Paternal MOPS scores of PCL-R Total scores (up to 10%) and PCL-R Interpersonal/Affective scores (up to 9%) in incarcerated adults. In addition, the same allele was associated with higher APSD-CU scores (5.65±2.52) as compared to C/C genotype (3.75±2.01) in CD youths exposed to active maltreatment. Overall, these data suggest that the interaction between *ANKK1* rs1800497 T allele and childhood maltreatment may increase the risk of affective deficits in different ages of life.

The *ANKK1* rs1800497 T allele has been previously associated with higher PCL-R Interpersonal/Affective scores in alcoholic patients (Hoenicka et al., 2007) and with CD in children (Beaver et al., 2007). Moreover, a significant interaction between *ANKK1* rs1800497 T allele and aversive experiences has been observed in association with antisocial behavior (Bakermans-Kranenburg & van Ijzendoorn, 2011; Beaver et al., 2012), as well as offenders carrying this allele, born from criminal fathers, showed persistent and violent delinquency (De Lisi et al., 2009). The *ANKK1* rs1800497 T allele has been also hypothesized to impair the capability to inhibit actions with negative consequences, that is a characteristic observed in both youths with CU traits (Pardini et al., 2012; Centifanti, 2012) and offenders with psychopathic traits (von Borries et al., 2010). Carriers of the *ANKK1* rs1800497 T allele have been shown to avoid actions with negative consequences significantly less frequently than C/C genotype carriers (Klein et al., 2007).

ANKK1 rs1800497 is a C/T change located in the gene coding for the Ankyrin Repeat and Kinase Domain Containing1 serine/tyrosine protein kinase. The *ANKK1* rs1800497 T allele impairs both the inhibition of dopamine (DA) release in the synapsis and DA reuptake by presynaptic transporters (Bolan et al., 2007; Lee et al., 2007). In particular, the *ANKK1* rs1800497 T allele has been associated with lower density of presynaptic inhibitory DA receptors 2 (DRD2) and higher DA availability in the striatum (Ritchie & Noble, 2003; Savitz et al., 2013; Eisenstein et al., 2016). Moreover, the *ANKK1* rs1800497 T allele has been shown to promote the uptake of the DA precursor L-DOPA by the striatum (Laakso et al., 2005) as compared to the *ANKK1* rs1800497 C/C genotype. The higher L-DOPA uptake, observed in the striatum of *ANKK1* rs1800497 T allele carriers, has been hypothesized to reflect a higher activity of the aromatic L-amino acid decarboxylase, which is the final enzyme in the biosynthesis of DA, thus consequently increasing DA synthesis (Laakso et al., 2005) and striatal activity (Siessmeier, et al., 2006; Burgorf et al., 2007). Interestingly, increased ventral striatum activity has been associated with higher PCL-R Factor 1 scores in a sample of incarcerated men (Docety et al., 2013).

In addition, both pharmacological and genetically driven increases of DA availability have been associated with reduced empathy (Crockett et al., 2015; Gong et al., 2014), which is a core

featureof both CU traits (Milone et al., 2019) and of the Interpersonal/Affective dimension of psychopathy (Hare, 2003). Anterior cingulate cortex, which has a central role in the regulation of empathic abilities (van Dogen, 2020), expresses DRD2s (Martres et al., 1985; Pazos et al., 1985; Ko et al., 2009), and pharmacological inhibition of DRD2s in this brain areahas been shown to reduce the empathic behavior in mice (Kim et al., 2014).

Based on these literature data, the results obtained in thepresent study suggest that the *ANKK1* rs1800497-mediated increase of dopaminergic signaling in the striatum, as well as in the ACC, might underlie the lack of empathy of both CU-children and adults with psychopathy. Moreover, as childhood maltreatment has been shown to increase the methylation of *ANKK1* (Cicchetti et al., 2016), we hypothesized that paternal maltreatment might further increase the *ANKK1* rs1800497-mediated potentiation of the dopaminergic signaling.

ANKK1 rs1800497 significantly interacted with *5-HTR1B* rs13212041 both in incarcerated adults and CD youths. On the one hand, in incarcerated adults with both *ANKK1* rs1800497 T allele and *5-HTR1B* rs13212041 T/T genotype, we observed a further increase of the variances of PCL-R Total scores (up to 16.2%) and PCL-R Interpersonal/Affective scores (up to 11.5%) explained by Paternal MOPS scores. On the other hand, the same combination of genotypes was associated with a further increase of APSD-CU scores (up to 6.17±2.37) in CD youths exposed to active maltreatment. Of note, as an APSD-CU subscale score of 6 is the cut-off above which CU traits are considered clinically relevant, we hypothesized that youths with CD carrying both *ANKK1* rs1800497 T allele and *5-HTR1B* rs13212041 T/T genotype have a clinically significant risk of developing CU traits if exposed to active maltreatment.

Interactions among dopaminergic and serotonergic polymorphisms have been previously shown to significantly affect behavior. For example, the co-occurrence of *COMT* rs4680 A allele, associated with reduced enzymatic activity (Strous et al., 1997; Mannisto & Kaakkola, 1999; Chen et al., 2004), and 5-HTTLPR S allele, associated with reduced 5-HT transporter expression (Heils et al., 1996), leading to higher extracellular concentration of DA and 5-HT, respectively, has been found associated with Borderline Personality Disorder (BPD) (Tadic et al., 2009). Of note, BDP shares some interpersonal/affective deficits with psychopathy in the presence of elevated antisocial lifestyle (Sprague et al., 2012).

The firing of serotonergic neurons in the Dorsal Raphe Nuclei is inhibited by D2 hetero-receptors expressed on their surface (Cai et al., 2022) and the reduced expression of these specific DRD2s may thus results in higher serotonergic signaling to mesocorticolimbic regions (Ma & Han, 1991-1815148). Serotonergic neuronal projections originating from the Dorsal Raphe Nuclei, indeed, interact with dopaminergic neurons in the Ventral Tegmental Area, which project to the

mesocorticolimbic system exerting an excitatory effect on dopaminergic neurons, as observed in the Nucleus Accumbens of the ventral striatum (Wang et al., 2019; Nagai et al., 2020). The Anterior cingulate cortex projects to the Nucleus Accumbens (Baliki et al., 2010; Gao et al., 2020), and the Anterior cingulate cortex→ Nucleus Accumbens circuit has been shown to be involved in empathic behavior (Smith et al., 2021). The Nucleus Accumbens controls guilt and reward anticipation, a motivational state that promotes actions associated with the expectation of a potential reward (Knusto & Greer, 2008; Dreher & Tremblay, 2009; Apaydin et al., 2018). More in details, increased Nucleus Accumbens activation has been shown to promote impulsive antisocial behavior during reward anticipation (Beck et al., 2009; Bucholtz et al., 2010) and inhibit guilt in the perspective of harming others (Chang et al., 2011). Individuals with psychopathic traits are known to seek reward (Byrd et al., 2014), be not worried by the prospect of harming others (Hare, 2003; Gong et al., 2019), and even deem the discomfort of others rewarding, pleasant, and stimulating (Docety et al., 2013).

We thus hypothesized that the *5-HTR1B* rs13212041 T/T genotype-mediated increase of serotonergic signaling may further increase DA release in the Nucleus Accumbens potentiating the *ANKK1* rs1800497 T allele-mediated increase of dopaminergic neurotransmission. In addition, the *ANKK1* rs1800497 T allele-mediated reduction of D2 hetero-receptors on serotonergic neurons in the DRN might further increase the serotonergic signaling to the Nucleus Accumbens. Thus, these interactions might underlie the lack of empathy and guilt observed in both children with CU traits and adults with psychopathy.

With regard to *TH* rs6356, the G/G genotype significantly increased the variances of PCL-R Total scores (up to 13.9%) and PCL-R Interpersonal/Affective scores (up to 13.7%) explained by Paternal MOPS scores in incarcerated adults. *TH* rs6356 is a nonsynonymous A/G change in the 2nd exon of the gene coding for the tyrosine hydroxylase that catalyzes the conversion of tyrosine to L-DOPA. The amino acid substitution due to the *TH* rs6356 is believed to fall into a regulatory domain; however, the function of this SNP in the brain is still uncertain. The Genotype-Tissue Expression (GTEx) database, collecting tissue-specific effects of genetic polymorphisms on gene expression in 54 different tissues from about 1000 healthy individuals, showed that the A/A genotype is significantly associated with a higher expression of *TH* in post-mortem skin samples (https://gtexportal.org/home/snp/rs6356), while similar, but not significant, trends have been observed in several brain regions.

TH rs6356 has been never investigated before in association with psychopathic traits, however its association with alcohol abuse has been described (Celorrio et al., 2012), and other

evidence has shown that alcohol abuse is often observed in people with CU traits or psychopathy (Craig et al., 2021).

The *TH* rs6356 G/G genotype significantly interacted with the *ANKK1* rs1800497 T allele. More in details, the co-occurrence of the *TH* rs6356 G/G genotype and the *ANKK1* rs1800497 T allele further increased the variance of PCL-R Total scores (up to 35.4%) explained by Paternal MOPS scores. Therefore, *TH* rs6356 G/G genotype by *ANKK1* rs1800497 T allele interaction seems to further increase the risk of psychopathy in subjects with a history of paternal maltreatment. As the functional effect of *TH* rs6356 is not clear, we speculated that the *TH* rs6356 G/G genotype might further increase the availability of DA, thus reinforcing the effect of the *ANKK1* rs1800497 T allele.

Moreover, the *TH* rs6356 G/G genotype by *ANKK1* rs1800497 T allele by *5-HTR1B* rs13212041 T/T genotype interaction was associated with an even higher increase of the variance of PCL-R Total scores (up to 43%) explained by Paternal MOPS scores.

These results suggest that, in association with paternal maltreatment, carrying all these three risk genotypes (*TH* rs6356 G/G genotype, *ANKK1* rs1800497 T allele and *5-HTR1B* rs13212041 T/T genotype) confers a higher risk of psychopathy than carrying only the *ANKK1* rs1800497 T allele in combination with the *TH* rs6356 G/G genotype or the *ANKK1* rs1800497 T allele in combination with the *5-HTR1B* rs13212041T/T genotype.

Finally, as far as the oxytocinergic pathway is concerned, in incarcerated adults, the *OXTR* rs53576 A allele significantly increased the variances of PCL-R Total scores (up to 7.3%), PCL-R Interpersonal/Affective scores (up to 5%), and PCL-R Lifestyle/Antisocial scores (up to 5.3%) explained by Paternal MOPS scores.

In line with these results, the *OXTR* rs53576 A allele has been previously found associated with psychopathy in a sample of incarcerated adults with mixed ethnicity (48% African-American, 36% Caucasian, 7% "mixed ethnicity", and 8% either Asian, Hispanic, Native American or others) (Verona et al., 2018) and with CU traits in children exposed to stressful life events (Ezpeleta et al., 2019). *OXTR* rs53576 is a G/A change in the 3rd intron of the gene coding for the oxytocin receptor (OXTR), whose functional role is not yet known (de Oliveira Pereira Ribeiro et al., 2018). However, the GTEx database shows that the A allele is significantly associated with an increased expression of OXTR mRNA in several brain regions, including the caudate, Nucleus Accumbens, cortex, putamen, frontal cortex, and hippocampus (https://gtexportal.org/home/snp/rs53576). OXTR has been extensively investigated in association with several aspects of social behavior, both positive, including empathy, attachment, prosocial behavior, and negative, like aggression and violence (for instance see Palumbo et al., 2018; Tops et al., 2019). The dual effect of OXT, which

appears to promote both prosocial and antisocial behaviors,has been explained by the "social salience hypothesis", which suggests that OXT broadly facilitates the perception and recognition of socially relevant cues; thus, OXT seems to potentiate the emotional responses to both positive and negative environmental stimuli, resulting in more positive and altruistic behaviors, or more negative and antisocial behaviors, respectively (Shamay-Tsoory & Abu-Akel, 2016).

Childhood maltreatment has been reported to increase urinary OXT levels (Seltzer et al., 2014), while the *OXTR* rs53576 A allele increased the vulnerability to adverse experiences and has been associated with a higher risk of negative outcomes (Byrd et al., 2021).

The *OXTR* rs53576 A allele carriers showed a reduced *OXTR* methylation greater than the G/G genotype carriers (Smearman et al., 2016). We thus hypothesized that carriers of the *OXTR* rs53576 A allele might be more vulnerable to paternal maltreatment as compared to the G/G genotype carriers, because maltreatment may potentiate the *OXTR* rs53576 A allele-induced increase of OXTR expression in the brain through a further reduction of the *OXTR* methylation, thus making these subjects more susceptible to both interpersonal/affective deficits and antisocial lifestyle.

The *OXTR* rs53576A allele significantly interacted either with *ANKK1* rs1800497 T allele, or *5-HTR1B* rs13212041 T/T genotype, or *TH* rs6356 G/G genotype separately. More in details, the variance of PCL-R Total scores explained by Paternal MOPS scores were further increased by the *OXTR* rs53576 A allele by *5-HTR1B* rs13212041 T/T genotype interaction (up to 16.2%), or *OXTR* rs53576 A allele by *ANKK1* rs1800497 T allele interaction (up to 16.1%), or *OXTR* rs53576 A allele by *TH* rs6356 G/G genotype interaction (up to 22.1%), as compared to the separated effects of *OXTR* rs53576 A allele (7.3%), *ANKK1* rs1800497 T allele (10%), *5-HTR1B* rs13212041 T/T genotype (7.4%), and *TH* rs6356 G/G genotype (13.9%).

Moreover, the *OXTR* rs53576 A allele by *5-HTR1B* rs13212041 T/T genotype by *TH* rs6356 G/G genotype interaction further increased the variance explained by Paternal MOPS scores of PCL-R Total scores (up to 39%).

OXT has been shown to have an excitatory effect on DA release in the mesocorticolimbic system, which is also involved in salience coding of signals and in attention-reorientation toward or away from external cues (Shamay-Tsoory & Abu-Akel, 2016). OXTR is also expressed in the raphe nuclei, where it directly interacts with the serotonergic neurons present in this brain area. More in details, the binding of OXT with the OXTRs in the raphe nuclei seems to promote the release of 5-HT (Yoshida et al., 2009). Therefore, an *OXTR* rs53576 A allele-mediated increase of OXTR levels in the brain might further increase the *5-HTR1B* rs13212041 T/T genotype, *TH* rs6356 G/G genotype or *ANKK1* rs1800497 T allele – mediated increase of extracellular levels of 5-HT and DA, with worse behavioral outcomes in carriers also exposed to maltreatment.

All the additional combinations of the *OXTR* rs53576 A allele with the other genetic variants, although significant, slightly increased the variance of PCL-R Total scores explained by Paternal MOPS scores, making their further contribution to the risk of psychopathy neglectable.

5.2 Limitations of the study

The current study has some potential limitations. First, a candidate gene approach was used, which could be prone to a high chance of false positive results (Tabor & Myers, 2002; Montgomery, 2020). However, it noteworthy that the selection of candidate genes was based on solid literature hypotheses linking these allelic variants to several aspects that characterize the investigated phenotypes (Iofrida, Palumbo & Pellegrini, 2014; Moore et al., 2019). Moreover, a stringent Bonferroni correction of the obtained p-values was applied to minimize the rate of type I errors. Our samples were not numerically adequate for GWAS (Mehta & Czamara, 2019), which are usually performed on several dozen thousands of subjects. However, our samples consisted of well-characterized incarcerated adults and adolescents and children with CD, which are not easy to collect.

Several additional factors that potentially increase the chance of Type I errors need be mentioned. For example, the participants belong to genetically different populations: the two forensic samples are from the US, whereas the clinical sample of youths is from Italy. Additionally, information about ethnicity was available only for the forensic samples, for whome self-reported ethnicity (i.e., Latin/Hispanic or not-Latin/Hispanic) had been previously collected. It is important to note that ethnicity can be accurately determined only through genomic sequencing. Therefore, the heterogeneity due to ancestry and cultural differences could have inflated the risk of false positive results (Freedman et al., 2004; Miller & Bersoff, 1992; Han, 2015).

The allele frequencies observed in our forensic and clinical samples were similar to the ones reported by 1000Genomes for the European-ancestry population. However, we observed statistically significant differences in the frequencies of some genotype groupings between Latin/Hispanics and not-Latin/Hispanics. Nevertheless, the effect of genetics on psychopathy observed in the whole samples went in the same direction in both Latin/Hispanics and not-Latin/Hispanics, even if some p-values were not statistically significant. The lack of significance was probably due to a drastic reduction of the sample size, with negative consequences on the statistical power of the analyses. For these reasons, ethnicity was used as a covariate.

What makes the studied samples particularly interesting, that is being forensic samples, also represents the second limitation of the present work. Indeed, both adult and adolescent offenders included a much higher percentage of subjects with psychopathic traits compared to the general population, which does not allow us to generalize the obtained results. Therefore, the psychopathy variance explained by genetics observed in our sample cannot be taken as representative of the entire population. Moreover, several differences have been highlighted between incarcerated

subjects with psychopathic traits and non-institutionalized individuals with psychopathy (Gao & Raine, 2010). These latter, indeed, are characterized by "successful psychopathy" and have intact or even enhanced brain functioning that underlies normal or superior cognitive abilities. This allows them to achive their goals through non-violent strategies. In contrast, incarcerated individuals are characterized by "unsuccessful psychopathy", and show brain structural and functional impairments, as well as dysfunction of the autonomic nervous system (Gao & Raine, 2010). These impairments might underlie cognitive and emotional deficits that predispose them to violent offending (Gao & Raine, 2010).

5.3 Conclusions and future perspectives

In summary, the results of this thesis work suggest that:

1) the *5-HTR1B* rs13212041 T/T genotype is a risk allele for high psychopathy scores with a direct effect on phenotype both in adults and adolescents;
2) paternal maltreatment is associated with psychopathy scores and that this association is higher in interaction with the *5-HTR1B* rs13212041 T/T genotype, the *ANKK1* rs1800497 T allele, the *OXTR* rs53576 A allele, and the *TH* rs6356 G/G genotype;
3) specific combinations of these risk alleles (*5-HTR1B* rs13212041 T/T genotype by *ANKK1* rs1800497 T allele by *TH* rs6356 G/G genotype and *5-HTR1B* rs13212041 T/T by *TH* rs6356 G/G genotype by *OXTR* rs53576 A allele) synergistically increase the association between paternal maltreatment and high psychopathy scores;
4) the *5-HTR1B* rs13212041 T/T genotype by the *ANKK1* rs1800497 T allele combination, in interaction with active maltreatment, predisposes to clinically relevant CU traits that overcome the diagnostic cut-off of the APSD-CU subscale.

Overall, these findings indicate that the combination of the *5-HTR1B* rs13212041 T/T genotype and the *ANKK1* rs1800497 T allele, in subjects exposed to childhood maltreatment, correlates with psychopathic traits from childhood to adulthood and might be an early predictor of psychopathy.
Given the functional role of these two alleles, the identified genetic profile should increase serotonergic and dopaminergic transmissionin several brain regions important for the development of social skills. I hypothesized that this genetically induced potentiation of neurotransmission makes children more vulnerable to maltreatment, thus increasing their risk of developing psychopathic traits.

Regarding the potential ethical and legal implications of the obtained results, it is important to highlight that they are not intended to suggest the introduction of preventive interventions for crimes that have not yet been committed. While CD youths with CU traits tend to exhibit more severe and persistent antisocial behavior (Bamvita et al., 2021), the presence of specific allelic variants that appear to be associated with high levels of psychopathy in criminals cannot predict future criminal behavior.

Nevertheless, our findings might have important clinical implications as they could help identify promptly the most vulnerable youths among children with CD and CU traits which show poor response to traditional treatments (Högström et al., 2013). Timely interventions could be crucial for these individuals, as treatments are tipically more effective when administered in the early stages of life when morality, empathic behavior, and caring attitudes are developing (Ellis,

1990; Dunn, Brown, & Maguire, 1995; Decety & Svetlova, 2012). However, the influence of single polymorphisms on human behavior is weak, so the presence of a specific risk genotype for psychopathic traits does not assume that treatment should be administered. It is well-known that the influence of genetic variants on behavior is stronger when in interaction with an aversive environment (Belsky et al., 2009; van Ijzendoorn et al., 2012). Thus, the presence of specific risk genotypes becomes more informative about their influence on psychopathy is the presence of childhood negative experiences, such as negative parenting. Current interventions for behavioral problems in youths are mostly based on parent training (Serketich & Dumas, 1996; NICE, 2006). CD youths with CU traits that carry specific risk genotypes would need preventive behavioral treatments tailored to reduce their affective deficits and re-educate parental behavior.

Regarding this matter, a novel therapeutic plan has been recently developed specifically targeted for CD youths with CU traits, consisting of the Parent–Child Interaction Therapy and Coaching and Rewarding Emotional Skills module. The first consists in teaching parenting skills to enhance the parent-child relationship through the use of verbal and physical expression of warmth, and training parents in reward-based behavior modification systems to motivate and reinforce positive child behavior (Kimonis et al., 2019). The second aims to improve child emotion recognition and understanding and reinforce prosocial and empathic behavior (Datyner et al., 2016; Kimonis et al., 2019). Interestingly, this specific treatment has been reported to increased empathy and reduce CU traits in children, maintained at a 3-month follow-up (Kimonis et al., 2019).

Future perspectives of my thesis work will be increasing the sample of children with CD to strength the statistical power of the study and recruiting an independent cohort of adolescents with externalizing problems to also collect childhood maltreatment data in line with what we did with the adult sample. Moreover, thanks to a recently obtained research grant, the exome-sequencing of all the three groups of subjects will be done to identify, starting from databases of Transcriptome Wide Association Studies (TWAS) in postmortem brains, polymorphisms associated with gene expression patterns to be combined into genetic profiles predictive of psychopathic traits with larger effect sizes as compared to single SNPs.

At last, as racial and ethnic minorities are to date poorly represented in genetic association studies (Suther & Kiros, 2009) we also plan to extend our study to black people, as well as to females.

Chapter 6

Appendices

6.1 Appendix A: Psychopathy Checklist-Revised (PCL-R)

The PCL-R is a 20-item questionnaire based on a clinical semi-structured interview with 125 questions used to measure psychopathy in incarcerated adults across the following two dimensions:

- PCL-R Factor 1
    - Facet 1 (Interpersonal) items 1, 2, 4, 5
    - Facet 2 (Affective) items 6, 7, 8, 16
- PCL-R Factor 2
    - Facet 3 (Behavioral) items 3, 9, 13, 14, 15
    - Facet 4 (Antisocial) items 10, 12, 18, 19, 20

Item 1. Glibness/superficial charm **0** **1** **2** **Omitted**

Item 2. Grandiose sense of self-worth **0** **1** **2** **Omitted**

Item 3. Need for stimulation **0** **1** **2** **Omitted**

Item 4. Pathological lying **0** **1** **2** **Omitted**

Item 5. Conning/manipulative **0** **1** **2** **Omitted**

Item 6. Lack of remorse or guilt **0** **1** **2** **Omitted**

Item 7. Shallow affect **0** **1** **2** **Omitted**

Item 8. Callous/lack of empathy **0** **1** **2** **Omitted**

Item 9. Parasitic lifestyle **0** **1** **2** **Omitted**

Item 10. Poor behavioral control **0** **1** **2** **Omitted**

Item 11. Promiscuous sexual behavior **0** **1** **2** **Omitted**

Item 12. Early behavioral problems **0** **1** **2** **Omitted**

Item 13. Lack of realistic long-term goals **0** **1** **2** **Omitted**

Item 14. Impulsivity **0** **1** **2** **Omitted**

Item 15. Irresponsibility **0** **1** **2** **Omitted**

Item 16.Failure to accept responsibility **0** **1** **2** **Omitted**

Item 17. Many short-term relationships **0** **1** **2** **Omitted**

Item 18. Juvenile delinquency **0** **1** **2** **Omitted**

Item 19. Revocation of conditional release **0** **1** **2** **Omitted**

Item 20. Criminal versatility **0** **1** **2** **Omitted**

6.2 Appendix B: Psychopathy Checklist-Youth Version (PCY:YV)

The PCL:YV is a 20-item questionnaire based on a clinical semi-structured interview with 125 questions used to measure psychopathy in incarcerated adolescents across the following twodimensions:

- PCL:YV Factor 1
    - Facet 1 (Interpersonal) items 1, 2, 4, 5
    - Facet 2 (Affective) items 6, 7, 8, 16
- PCL:YV Factor 2
    - Facet 3 (Behavioral) items 3, 9, 13, 14, 15
    - Facet 4 (Antisocial) items 10, 12, 18, 19, 20

Item 1. Impression management	**0**	**1**	**2**	**X**
Item 2. Grandiose sense of self worth	**0**	**1**	**2**	**X**
Item 3. Stimulation seeking	**0**	**1**	**2**	**X**
Item 4. Pathological lying	**0**	**1**	**2**	**X**
Item 5. Manipulation for personal gain	**0**	**1**	**2**	**X**
Item 6. Lack of remorse	**0**	**1**	**2**	**X**
Item 7. Shallow affect	**0**	**1**	**2**	**X**
Item 8. Callous/lack of empathy	**0**	**1**	**2**	**X**
Item 9. Parasitic orientation	**0**	**1**	**2**	**X**
Item 10. Poor anger control	**0**	**1**	**2**	**X**

Item 11. Impersonal sexual behavior	**0**	**1**	**2**	**X**
Item 12. Early behavior problems	**0**	**1**	**2**	**X**
Item 13. Lacks goals	**0**	**1**	**2**	**X**
Item 14. Impulsivity	**0**	**1**	**2**	**X**
Item 15. Irresponsibility	**0**	**1**	**2**	**X**
Item 16. Failure to accept responsibility	**0**	**1**	**2**	**X**
Item 17. Unstable interpersonal relationships	**0**	**1**	**2**	**X**
Item 18. Serious criminal behavior	**0**	**1**	**2**	**X**
Item 19. Serious violations of conditional release	**0**	**1**	**2**	**X**
Item 20. Criminal versatility	**0**	**1**	**2**	**X**

6.3 Appendix C: Antisocial Process Screening Device (APSD) parent version

The APSD is a 20-item parent-report questionnaire used to measure psychopathic traits in youths across the following three measures:

• Narcissism

• Callous unemotional traits

• Impulsiveness

Scoring instructions:

Items 5, 8, 10, 11, 14, 15, 16 relate to the 'Narcissism' measure

Items 3, 7, 12, 18, 19, 20 relate to the 'Callous unemotional traits' measure

Items 1, 4, 9, 13, 17, relate to the 'Impulsiveness' measure.

Rate each statement either as:

Never true= 0

Sometimes true= 1

Often true= 2

Sum the scores of the responses to items in each of the three categories to produce a total score for each category. The 'Callous unemotional traits' category has a cut-off score of six (Frick & Hare, 2001).

There is no cut-off score for the total score; the total score provides a dimensional measure showing the degree to which the child shows psychopathy traits.

	score
1. Blames others for mistakes	□
2. Engages in illegal activities	□
3. Cares about schoolwork*	□
4. Acts without thinking	□
5. Emotions are fake	□
6. Lies easily	□
7. Good at keeping promises*	□
8. Brags about abilities	□
9. Gets bored easily	□
10. Cons others to get what youwant	□
11. Teases/makes fun of others	□
12. Feels bad when do something wrong*	□
13. Does risky things	□
14. Acts charming to get things	□
15. Gets angry when corrected	□

16. More important than others □
17. Does not plan ahead □
18. Concerned about the feelings of others* □
19. Hides feelings from others □
20. Keeps same friends* □

*Reverse scored.

6.4 Appendix D: Measure of Parental Style (MOPS)

The MOPS is a self-assessment tool used to measure perceived parenting styles across the following three measures:

• Indifference

• Abuse

• Overcontrol

Scoring instructions:

Items 5, 8, 10, 11, 12, 13 relate to the 'Indifference' measure

Items 2, 7, 9, 14, 15 relate to the 'Abuse' measure

Items 1, 3, 4, 6 relate to the 'Overcontrol' measure.

Sum the scores of the responses to items in each of the three categories to produce a total score for each category.The total score for each parent provides a dimensional measure showing the degree to which parenting style of each parent was experienced by an individual. There is no cut-off score.

Reference:

Parker, G., Roussos, J., Hadzi-Pavlovic, D., Mitchell, P., Wilhelm, K. and Austin, M-P. (1997) The development of a refined measure of dysfunctional parenting and assessment of its relevance in patients with affective disorders. Psychological Medicine, 1997, 27, 1193-1203.

Black Dog Institute – Measure of Parental Style (MOPS)

http://www.blackdoginstitute.org.au/

During your first 16 years how 'true' are the following statements about your mother's, or Father's behavior towards you

Rate each statement either as:
0 - not true at all
1 - slightly true
2 - moderately true
3 - extremely true

Mother:	**score**	**Father:**	**score**
1. Overprotective of me	□	1. Overprotective of me	□
2. Verbally abusive of me	□	2. Verbally abusive of me	□
3. Over controlling of me	□	3. Over controlling of me	□
4. Sought to make me feel guilty	□	4. Sought to make me feel guilty	□
5. Ignored me	□	5. Ignored me	□
6. Critical of me	□	6. Critical of me	□
7. Unpredictable towards me	□	7. Unpredictable towards me	□
8. Uncaring of me	□	8. Uncaring of me	□
9. Physically violent or abusive of me	□	9. Physically violent or abusive of me	□
10. Rejecting of me	□	10. Rejecting of me	□
11. Left me on my own a lot	□	11. Left me on my own a lot	□
12. Would forget about me	□	12. Would forget about me	□
13. Was uninterested in me	□	13. Was uninterested in me	□
14. Made me feel in danger	□	14. Made me feel in danger	□
15. Made me feel unsafe	□	15. Made me feel unsafe	□

6.5 Appendix E: Maltreatment Index (MI) Clinician-report form

The MI is clinical-report interview measuring three types of childhood maltreatment:

- Emotional abuse
- Physical abuse
- Neglect

Scoring instructions:

The score for each category provides a dimensional measure showing the degree of different types of child maltreatment by parents.

Sum the scores of the emotional abuse and physical abuse to produce a score of "active maltreatment".

The total score provides a dimensional measure showing the degree to which parent maltreated their child.

- There is no cut-off score.

The following questions ask about some things that may or may not have been experienced by this client when they were a child or more recently. Please answer whether any of these items are relevant to this client based on whether this has ever happened to them.

Please do not record the client's name on this form.

Has this client ever experienced the following from their parent, guardian, or another trusted adult known to them?

	Never	**A little bit**	**A fair bit**	**All the time**
Emotional abuse				
Being belittled or ridiculed; fear or intimidation; being blamed inappropriately; extreme negativity and hostility; exposure to violence; abandonment; being confined in an enclosed space; threats of violence.	□	□	□	□
Neglect				
Being left without supervision; not being given enough to eat; not having enough clothing and/or shelter; not having enough medical treatment; being exposed to weapons; being left in the care of dangerous people; being exposed to criminal activity; not being sent to school.	□	□	□	□

Physical abuse

Being physically injured in a non-accidental way: being hit; being bruised; being choked; being burnt; having bones broken.	□	□	□	□

Based on your knowledge of this client and his/her history, please indicate the level of confidence you have in the responses given above:

Low confidence Moderate confidence High confidence

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