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RESEARCH ARTICLE

Association between S-COMT activity and impulsive and premeditated aggression in a population of violent offenders: preliminary results of a cross sectional study [version 1; peer review: awaiting peer review]

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Abstract

Aggression can be conceptualised as a physical act towards another person, verbal offenses, destructive acts towards objects, and self-inflicted harmful acts. It is highly frequent in the context of Antisocial Personality Disorder (ASPD) and has been correlated to disturbances in the dopaminergic system. In the prefrontal cortex, the dopamine metabolism depends on catechol-O-methyltransferase (COMT). DRD2 receptors also play a role in the expression of aggression by modulating dopamine metabolism, in the striatum. In this study, we evaluated the association between COMT activity and type of aggression, in a sample of violent male offenders. Participants were subjected to sociodemographic, clinical, and psychometric evaluation through standardised instruments. Erythrocyte S-COMT activity was measured, and COMT and the DRD2 genotypes were analysed. Individuals displaying impulsive aggression showed lower S-COMT erythrocyte activity ($p=0.026$) and lower frequency of Val/Val (rs4680) genotype than individuals with premeditated aggression ($p=0.047$). S-COMT erythrocyte activity was positively correlated with the PCL-R total score ($r=0.34$; $p=0.018$). In conclusion, our preliminary results indicate that COMT can be associated to different aggression types in violent offenders, and it can represent a possible pharmacological target for the treatment of impulsive and premeditated aggression, in incarcerated patients.

Keywords

Aggression, COMT, Antisocial personality disorder, Impulsivity, BIS-11

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Introduction

Aggression can manifest itself through physical acts directed against other individuals, verbal offenses, destructive acts towards objects, and self-inflicted harmful acts (Siever, 2008). In this study, we limited aggression to physical aggression directed against another individual. An act of aggression can be categorized as impulsive or premeditated, with distinct manifestation over time; although there may be a predominant type (Meloy, 2006).

Aggression is part of several psychiatric syndromes and is particularly common in antisocial personality disorder (ASPD) (American Psychiatric Association, 2013), in which physical aggression is one of the core symptoms (Bourne, 2010). Aggressive behaviour conducts often to crime, with subsequent episodes of imprisonment (Pingault *et al.*, 2013). Nevertheless, even during periods of incarceration, aggressive behaviour is maintained (Morana, Arboleda-Flórez, & Câmara, 2005; Wolff, Blitz, Shi, Bachman, & Siegel, 2006). Some of these individuals express aggression since early childhood and pharmacotherapy has shown reduced efficacy (Felthous, Lake, Rundle, & Stanford, 2013). Overall, the individuals remain unable to reduce this behaviour through common learning and education. This reinforces the need for an effective assessment of the displayed aggression type, as well as for further research of biological targets for pharmacological intervention (Pingault *et al.*, 2013).

The most relevant predictors for aggression are criminal history, hostile behaviour, impulsivity, antisocial personality, recent drug or alcohol misuse, 'positive symptoms' of psychosis, and non-adherence to therapy (Farrington, 2011; Witt, van Dorn, & Fazel, 2013).

The relevance of the genetic study of human aggression is highlighted by the fact that aggression represents a behaviour that the human species has upheld over time, suggesting its evolutionary value (Wrangham, 2018). The heritability of aggressive behaviour can reach 50%, and genetic factors are related to the aetiology of aggression, in particular that starting in childhood (Blonigen & Krueger, 2005; Laucht, Brandeis, & Zohsel, 2013).

In a recent study, we have confirmed that, although impulsive aggression was predominant in a population of male ASPD offenders, those who showed higher scores of psychopathic traits were less prone to exhibit impulsive aggression, and tended to display premeditated aggression (J. Azevedo, Vieira-Coelho, Castelo-Branco, Coelho, & Figueiredo-Braga, 2020). An individual showing premeditated aggression can have a higher risk for aggression recidivism: in these cases, the use of pharmacological interventions has no positive results (Swogger, Walsh, Christie, Priddy, & Conner, 2015). Hence, it is mandatory to characterise the aggression type in offenders and find the biological variants that could be therapeutic targets.

The neurobiology of aggression in healthy and psychiatric populations has been associated with changes in the dopamine metabolism (Panasiuk, Hertz, & Gale-Grant, 2019; Rosell & Siever, 2015). The dopaminergic system function has been linked to angry-impulsive personality traits (Joyce *et al.*, 2009) and to a detached personality (Jönsson *et al.*, 2003). In humans, pharmacological agents which increase dopamine levels can lead to aggressive behaviour and impulse control disorders (Azevedo J, Esteves M, Rosas MJ, 2010; Canário *et al.*, 2019).

The dopamine metabolism in the prefrontal cortex (PFC) and limbic system depends mostly on the Catechol-O-methyltransferase (COMT) activity. The enzymatic activity of COMT, including S-COMT, has been associated with physical aggression in several studies, opening several possibilities for future research on the utility of this enzyme as a target for the treatment of several dysfunctions (Craig & Halton, 2009; Volavka *et al.*, 1997).

The most analysed COMT polymorphism is the COMT Val¹⁵⁸Met (rs4680) that is distributed in Caucasian populations as follows: Met/Met 28%, Met/Val 51%, Val/Val 21% (González-Castro *et al.*, 2013). This polymorphism (responsible for a decrease in COMT activity) has been associated with aggression in different psychiatric populations. For example, the Met/Met genotype (lower enzymatic activity of COMT) has been associated with aggression in schizophrenia patients (Han, Park, Na, Kee, & Lee, 2004). Conversely, the Val/Val genotype (higher enzymatic activity of COMT) is associated to aggression in samples of patients with attention deficit hyperactivity disorder (ADHD) and extreme antisocial behaviour (Langley, Heron, O'Donovan, Owen, & Thapar, 2010). These contradictory results may be due to the lack of clinical characterization and definition of the type of aggression, in the studied samples, and to the possible variation of frequency of the distribution of this COMT polymorphism, in different populations (Reidy *et al.*, 2017). The role of COMT activity in decision-making processes, through the modelling of the availability of dopamine in the PFC, could predict the type of aggression.

It has been proposed that antisocial individuals, having the Met/Met genotype, may present stable cognitive performance and preserved emotional functioning, but lower resistance to emotional stress, being more sensitive to social rejection and

to the need of reward (Yildirim & Derksen, 2015). On the other hand, it has also been proposed that antisocial individuals with the Val/Val genotype would show reduced cognitive performance, emotional insensitivity, higher resistance to emotional stress, and insensitivity to social rejection and reward (Yildirim & Derksen, 2015). These theoretical proposals may suggest that antisocial individuals with the Val/Val genotype may display more psychopathic personality traits related to emotional insensitivity measured by the facets interpersonal (F1) and affective (F2) of the Psychopathic Checklist-Revised (PCL-R) (Hare, 2003). These personality traits have been consistently pointed out as predictors of premeditated aggression in individuals with extreme antisocial behaviour (J. Azevedo *et al.*, 2020).

The COMT Val¹⁵⁸Met polymorphism determines the dopamine concentration in the PFC, but not in the striatum (Hirvonen *et al.*, 2010). In fact, we can find only a few dopamine D2 receptors in the PFC (MISSALE, NASH, ROBINSON, JABER, & CARON, 1998). However, they are abundant in the striatum, meaning that, to evaluate the dopaminergic component of aggression we should also analyse dopamine receptors. The A1 (T) allele of dopamine D2 receptor/ankyrin repeat and kinase domain containing 1 (*DRD2/ANKK1*) TaqIA (rs1800497) single nucleotide polymorphism has been associated with reduced striatal D2/D3 receptor availability. This genetic variant has been referred to contribute to significant individual differences in human striatal function, neuropsychiatric disease risk, and pharmacological response (Eisenstein *et al.*, 2016). It has been associated with addiction, impulsivity and antisocial personality traits (Ponce *et al.*, 2008; Rivera-Iñiguez, Panduro, Ramos-Lopez, Villaseñor-Bayardo, & Roman, 2019). In addition, it may also play a role in aggression due to its influence on psychopathy phenotypes (Ponce *et al.*, 2008).

Impulsive and premeditated aggression may be distinguished by biological, psychological, psychosocial, and clinical variables (Meyer, Cummings, Proctor, & Stahl, 2016). The dopaminergic system appears to be a relevant player in this distinction, informing the risk for aggression recidivism and the effectiveness of pharmacological interventions (Swogger *et al.*, 2015).

In this study, we aimed to evaluate the dopaminergic function in imprisoned violent offenders, through the assessment of the correlation between COMT activity and aggression type. For this, we used a cross sectional approach in a sample of violent male offenders and confirmed the results by genotyping.

Methods

Study population

This study was conducted in a medium/high security penal institution for male offenders, in the North of Portugal. The sample included 46 male inmates that were referred to the Psychiatry clinical services, after performing acts of physical aggression towards other inmates. The research protocol was approved by an Ethics Committee from Centro Hospitalar e Universitário de São João (Document number 48.14) and by the hosting institution, the General Directorate for Probation and Prison Services.

Subjects were recruited through the use of a convenience sampling strategy between January and March of 2015. The primary requirement for inclusion in the study was the evidence of acts of physical aggressions towards other inmates. Participants should also be over 18 years old. The ability to read and to provide their written informed consent was also taken into consideration. Participants were excluded if the aggression occurred in the context of an acute neurological disorder (e.g., epilepsy, confusional states) or as an acute episode of a major psychiatry disorder (e.g., non-organic psychosis, major depression).

In accordance with the Declaration of Helsinki, informed consent was obtained from the legal guardian of the subjects, after being elucidated about the procedures.

Procedures and instruments

The participants that agreed to participate were interviewed and went through a blood sample collection, in the clinical department of the penitentiary institution.

Individuals were diagnosed by a forensic psychiatrist (JA) using a standardised interview – the Mini-International Neuropsychiatric Interview (MINI). Participants were assessed by means of the Portuguese version (Amorim, Lecrubier, Weiller, Hergueta, & Sheehan, 1998; Lecrubier *et al.*, 1997). The psychometric assessment of participants included a battery of standardised instruments: the Psychopathy Checklist-Revised (PCL-R), the Barratt Impulsivity Scale Version 11 (BIS-11), and the Impulsive/Premeditated Aggression Scale (IPAS).

We opted for a cross sectional approach that allowed us to compare, at a specific point in time, two groups within our population: group P (individuals with premeditated aggression) and group I (individuals with impulsive aggression).

The biological variables of this study were S-COMT erythrocyte activity, and COMT Val¹⁵⁸Met (rs4680) and DRD2/ANKK1 TaqIA (rs1800497) polymorphisms.

Psychopathy Checklist-Revised (PCL-R)

The PCL-R measures psychopathic traits by collecting information from clinical records and applying a semi-structured interview (Hare, 2003). The 20 items that compose the PCL-R are scored as absent (0), present to some degree (1), or fully present (2), providing a maximum total score of 40 points. The PCL-R is a four-factor model comprising interpersonal, affective, lifestyle, and antisocial facets. The structural properties of PCL-R were previously validated in Portuguese samples (Gonçalves, 1999).

Barratt Impulsiveness Scale Version 11 (BIS-11)

The BIS-11 is a self-report questionnaire used for assessing general impulsivity (Patton, Stanford, & Barratt, 1995). The current scale version contains 30 items that are rated from 1 (rarely/never) to 4 (almost always/always). Factor analyses reveal six first-order factors (Attention, Cognitive Instability, Motor, Perseverance, Self-Control, and Cognitive Complexity), and three second-order factors (Attentional, Motor, and Non-planning). The structural properties of BIS-11 were replicated in Portuguese-speaking subjects (von Diemen, Szobot, Kessler, & Pechansky, 2007).

Impulsive/Premeditated Aggression Scale (IPAS)

IPAS is a 30-item self-report questionnaire used to rate aggressive acts that occurred over the previous six months (Stanford *et al.*, 2003). In details, participants were asked to complete the IPAS questionnaire considering their aggressive acts in the last 6 months. The questionnaire comprises fifteen items focused on impulsive aggressive (IA) characteristics and 15 items focused on premeditated aggressive (PM) characteristics. Items are scored on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).

IA and PM can be scored either dimensionally or categorically. To characterize aggressive behavior as predominately impulsive or premeditated, items for which the individual answered “strongly agree” or “agree” were rated as positive and the total number of positive items was then determined for both IA and PM scales. The aggressive behavior of those individuals showing a higher percentage of positive IA characteristics was characterized as predominately impulsive, whereas those showing a higher percentage of positive PM characteristics were characterized as predominately premeditated. Individuals showing the same percentage of positive IA and PM characteristics were not characterized.

The structural properties of IPAS were previously validated in the Portuguese forensic and general population (J. C. Azevedo, Pais-Ribeiro, Coelho, & Figueiredo-Braga, 2018; Cruz *et al.*, n.d.).

Erythrocyte soluble catechol-O-methyltransferase (S-COMT) assay

Erythrocyte S-COMT was obtained from washed erythrocytes submitted to haemolysis, as previously described (Amorim-Barbosa, Serrão, Brandão, & Vieira-Coelho, 2016). Venous blood samples were collected between 08.00 and 09.00 a.m., after an overnight fast, and kept on ice in K₃EDTA tubes, until processing. Blood samples were centrifuged at 1500 g, for 10 minutes at 4 °C; the plasma was removed and the uppermost cell layer was separated for genetic analysis. Afterwards, a volume of cold 0.9% NaCl solution was added to the erythrocytes and the mixture was gently vortexed. Thereafter, the tubes were centrifuged (at 1500 g, 10 minutes, 4 °C), and the supernatant was discarded. This process was repeated twice. Washed erythrocytes were stored at -70 °C, until the enzyme assay was carried out. On the day of the experiment, the frozen erythrocytes were thawed on ice.

Haemolysis was conducted at a ratio of 4:1 (water:erythrocytes; V:V). Following vigorous mixing, the tubes stood on ice for 10 minutes. Then, the tubes were centrifuged at 20,000 g, for 20 minutes at 4 °C, and the supernatant was collected for the assay of erythrocyte S-COMT. The protein content was determined using human serum albumin as standard (Bradford, 1976).

COMT activity was determined by the ability of enzyme preparations to methylate adrenaline to metanephrine. In the kinetic studies, COMT was incubated with concentrations of adrenaline of 3, 10, 30, 100, 300, 1000, and 3000 µmol L⁻¹. The reaction was stopped with perchloric acid. The samples were kept at 4 °C for two hours, and then centrifuged (5400 g, 10 minutes, 4 °C). 500 µl aliquots of the supernatant, filtered on 0.22 µm pore size Spin-X filter tubes (Costar), were used for the assay of metanephrine.

Assay of catechol derivatives

Aliquots of samples from the COMT assay were assayed for metanephrine by HPLC with electrochemical detection, as described by Vieira-Coelho (Vieira-Coelho & Soares-da-Silva, 1999). In brief, aliquots of 20 or 50 µL were injected into

the chromatograph. The chromatographic system consisted of a pump (Gilson 307) and a stainless steel 5 mm ODS2 column (Biophase; Bioanalytical Systems, West Lafayette, IN, USA), of 25 cm length and 4.6 mm diameter; samples were injected by means of an automatic sample injector (Gilson 231) connected to a Gilson dilutor (Gilson 401). The mobile phase was a degassed solution of citric acid 0.1 mM, sodium octylsulphate 0.5 mM, sodium acetate 0.1 M, Na₂EDTA 0.17 mM, dibutylamine 1 mM, and methanol (10 % v/v), adjusted to pH 3.5 with PCA 2 M and pumped at a rate of 1.0 mL/min. The detection was carried out electrochemically with a glassy carbon electrode, an Ag/AgCl reference electrode, and an amperometric detector (Gilson 142); the detector cell was operated at 0.75 V. The current produced was monitored using the Gilson Unipoint HPLC software. The lower limit of detection of metanephrine ranges from 350 to 1000 fmol.

Enzyme kinetics

The most common kind of enzyme kinetics experiment is to vary the concentration of substrate and measure enzyme velocity. The goal is to determine the enzyme's K_M and V_{max} according to the Michaelis-Menten model (Lorsch, 2014):

$$v = V_{max} [S] / (K_M + [S])$$

In which, V_{max} is the maximum enzyme velocity and represents the velocity of the enzyme extrapolated to very high concentrations of substrate, K_M is the Michaelis-Menten constant and represents the substrate concentration needed to achieve a half-maximum enzyme velocity and S is the substrate concentration.

Drugs

S-adenosyl-L-methionine, DL-metanephrine and adrenaline (bitartrate salt) were purchased from Sigma Chemical Co. (St Louis, MO).

DNA extraction

Genomic DNA extraction from leukocytes was performed following the manufacturer's instructions of the Quick-DNA Plus Kits (Zymoresearch, CA, USA). A 100 ng/ μ L DNA aliquot was stored at -80 °C until use.

Genotyping

Allelic discrimination for the COMT Val¹⁵⁸Met (rs4680) and DRD2/ANKK1 TaqIA (rs1800497) polymorphisms were determined through real-time polymerase chain reaction (PCR) technique, using a TaqMan SNP genotyping assay with fluorogenic probes (Applied Biosystems, Foster City, CA). Briefly, 15 ng of DNA was amplified in a total volume of 8 μ L containing 0.2 μ L of a minor groove binder (MGB) probe solution (Applied Biosystems) and 4 μ L of TaqMan universal polymerase chain reaction master mix (Applied Biosystems). PCR conditions were provided by the manufacturer: 40 cycles of 95°C denaturation (15 sec), 60°C anneal/extension (1 min).

Thermal cycling and fluorescence signal genotyping were performed through the StepOnePlus Real-Time PCR system (Applied Biosystems, Foster City, CA). A positive control for each possible genotype and a negative control were included in each 96-well plate.

Statistical analysis

Data were summarised using descriptive statistics: continuous variables are presented as mean (standard deviation) or median (interquartile range [Q1, Q3]), while categorical variables are presented as absolute or relative frequencies. Continuous variables were subjected to normality testing (Kolmogorov–Smirnov test) and, when the normality assumption was validated, Student T test, and Chi-square test were used to compare data in premeditated and impulsive aggression groups. When data did not meet the requirements of parametric tests, non-parametric Mann–Whitney was used. A p value of <0.05 was considered to be statistically significant (J. Azevedo *et al.*, 2020).

The degree of association between variables with normal distribution (COMT and PCL-R) was measured by the Spearman correlation coefficient.

A logistic regression analysis was employed to investigate the significant variables associated with the prediction of aggression categorisation using Vittinghoff's recommendations for small samples (Vittinghoff, Eric, McCulloch, Charles E, Glidden, David V, Shiboski, 2007). Using a forward, stepwise, conditional methodology, ASPD, PCL-R total score, facet 1 (interpersonal) and facet 2 (affective), S-COMT erythrocyte activity and COMT genotype were included in the analysis.

Michaelis–Menten constant (Km) and maximum velocity (Vmax) values for COMT activity were calculated by nonlinear regression analysis using the GraphPad Prism statistics software package, version 6.0 for Windows (GraphPad Software, La Jolla, CA, USA) (Amorim-Barbosa *et al.*, 2016). Statistical analysis was performed by one-way analysis of variance ANOVA using Newman–Keuls multiple comparison test to compare values ($p < 0.001$).

Analyses were carried out using IBM SPSS Statistics for Mac, Version 26.0 (Armonk, NY, USA: IBM Corp.).

Results

Sociodemographic and clinical characterisation

The sample comprised 46 offenders with a median age of 35 (Q1: 31, Q3: 41.5) years, of which 33 were single (72%), and 29 had children (63%). The median education level was 7.0 (Q1: 6.0; Q3: 9.5) years. At the time of assessment, the median length of imprisonment was 114.0 (Q1: 60.9; Q3: 175.5) months. Besides having committed aggressive acts towards other inmates, a total of 25 individuals (54%) had also a history of being convicted for violent crimes, such as physical assault, murder, or attempted murder.

Considering clinical psychiatric disorders in the entire sample, 34 offenders received the diagnosis of antisocial personality disorder (71%), 20 showed psychopathy (44%), 26 presented SUD (57%), 10 had depressive disorders (21%), and 14 displayed anxiety disorder (30%).

Results from aggression characterization (IPAS) showed that impulsive aggression was detected in 78.2 % of the participants ($n=36$), whereas the premeditated type was detected in 21.8% ($n=10$). Thus, offenders were allocated in two different groups according with the aggression type: Group I – individuals with impulsive aggression, and Group P – individuals with premeditated aggression.

Comparison between the impulsive and premeditated aggression groups

Both groups presented similar sociodemographic and criminal characteristics, as well as prevalence of substance use, depressive and anxiety disorders. In addition, both groups presented similar total BIS-11 scores, showing comparable values of attentional, motor, and non-planning dimensions of impulsivity (Table 1).

Table 1. Clinical and psychometric characteristics of the individuals from impulsive and premeditated aggression groups.

	Group I (n=36)	Group P (n=10)	p-value
Psychiatric disorders			
ASPD ¹	25 (70%)	9 (90%)	0.004^a
Substance use ¹	20 (57%)	5 (50%)	0.95 ^a
Depressive disorders ¹	9 (25%)	1 (10%)	0.39 ^a
Anxiety ¹	13 (36%)	1 (10 %)	0.16 ^a
PCL-R total²	24.7±8.0	34.8±5.7	0.001^b
F1-Interpersonal ³	6.0 (4.0, 8.0)	8.0 (4.5, 8.5)	0.011^c
F2-affective ³	4.0 (2.0, 6.0)	8.0 (6.0, 8.0)	0.014^c
F3-Lifestyle ³	8.0 (6.0, 10.0)	10.0 (7.5, 10.0)	0.09 ^c
F4-Antisocial ³	6.0 (4.0, 8.0)	10.0 (6.0, 10.0)	0.15 ^c
BIS-11 total³	56.0 (48.8, 70.0)	62.0 (49.0, 64.0)	0.87 ^c
Attentional ³	15.0 (11.0, 18.0)	15.0 (13.0, 15.0)	0.83 ^c
Motor ³	20.0 (15.0, 23.0)	19.0 (13.0, 21.0)	0.60 ^c
Non-planning ³	22.0 (17.0, 28.0)	20.0 (17.0, 25.0)	0.66 ^c

Group I – Individuals with impulsive aggression, Group P – Individuals with premeditated aggression.

ASPD: Antisocial personality disorder.

¹: n (%).

²: mean ± SD.

³: median (Q1; Q3).

^a: Chi-square Test.

^b: Student T test.

^c: Mann-Whitney Test.

In contrast, we found that offenders with premeditated type of aggression presented higher prevalence of ASPD ($p=0.004$), and a higher score for psychopathic traits given by total PCL-R ($p=0.001$), facet 1 ($p=0.011$) and 2 ($p=0.014$) scores, when comparing to impulsive aggression group (Table 1).

S-COMT erythrocyte activity and type of aggression

Erythrocyte S-COMT activity (pmol/mg prt/h) was significantly higher ($p<0.05$) in offenders with premeditated aggression (22 ± 5) than in those of the impulsive aggression group (18 ± 3). These results were obtained with a single concentration of substrate (adrenaline, 1000 μM), and although significant, the difference between groups was small and its impact was difficult to evaluate. Thus, we decided to characterise enzyme kinetics in 6 individuals from each group. In these experiments, increasing concentrations of adrenaline (1, 3, 10, 30, 100, 300, 1000 and 3000 μM) were used as substrate. Substrate versus velocity curves for Erythrocyte S-COMT activity are shown in Figure 1. Kinetic analyses revealed that the maximum enzyme velocity (V_{max}) value was significantly higher ($p=0.0001$) in offenders with premeditated aggression than in those with impulsive aggression (40.1 ± 2.4 vs 21.2 ± 1.2 pmol/mg prt/h). The K_m value (in μM) was similar in both groups (896 ± 141 vs 874 ± 136).

In addition, S-COMT activity showed to be a predictor of the BIS-11 score ($R^2=0.12$; $p=0.022$).

S-COMT erythrocyte activity and psychopathy

Considering all the sample ($n=46$), we found that S-COMT erythrocyte activity was positively correlated to PCL-R total score (Pearson correlation= 0.34 ; $p=0.018$), (Figure 2). However, we could not find any predictor of PCL-R.

COMT Val¹⁵⁸Met polymorphism

The sample comprised 4 individuals (8.7%) with the Met/Met genotype, 26 (56.5%) with the Met/Val, and 16 (34.8%) with the Val/Val genotype. The results regarding genotype were in agreement with the results of functional enzyme activity, since the S-COMT erythrocyte activity was lower in the Met/Met genotype individuals than in those with Met/Val, and also lower than those with Val/Val genotype ($p=0.0001$) (Figure 3).

Figure 1. Erythrocyte S-COMT activity (pmol/mg prt/h) in offenders with premeditated aggression and impulsive aggression, shown as the rate of formation of metanephrine (MN) with increasing concentrations (in μM) of adrenaline (AD).

Figure 2. S-COMT erythrocyte activity in pmol/mg prt/h plotted against PCL-R total score from 46 male offenders.

Figure 3. S-COMT erythrocyte activity (pmol/mg prt/h) according to the genotype for COMT Val¹⁵⁸Met polymorphism.

Furthermore, offenders with premeditated aggression had a higher prevalence of the Val/Val genotype than individuals with impulsive aggression ($p=0.047$).

DRD2/ANKK1 TaqIA polymorphism

Regarding the DRD2/ANKK1 TaqIA polymorphism, the sample comprised 13 (28.3%) individuals with A1 allele, with similar distribution in the impulsive and premeditated groups (22.0% vs 29.7%; $p=0.07$).

Potential predictive factors of aggression type

The premeditated and impulsive groups showed differences in ASPD, PCL-R total score, facet 1 (interpersonal) and facet 2 (affective), S-COMT erythrocyte activity and COMT genotype. As so, these variables were included in a logistic regression model performed with the objective of identifying potential predictive factors.

PCL-R reliably distinguished between impulsive and premeditated aggression (Chi-square=16.7; $p=0.001$; $df=1$; Nagelkerke's $R^2=0.55$). The exponential beta value for PCL-R was 1.44 (CI=1.12, 1.85), meaning that, for each increase in one unit of the PCL-R, the OD for premeditated aggression increased by 1.44.

Discussion

In this preliminary study, we have found that male offenders displaying impulsive aggression showed lower S-COMT erythrocyte activity than individuals with premeditated aggression. Due to the lack of previous evidence on this subject, we opted to further validate the obtained results by adding genetic studies to our initial investigation plan. The results evidenced that impulsive and premeditated aggression were associated with different genotypes of the COMT Val¹⁵⁸Met polymorphism and with S-COMT erythrocyte activity. In detail, individuals with premeditated aggression had a higher prevalence of the Val/Val genotype and showed higher values of erythrocyte S-COMT activity. In theory, these individuals may have lower DA availability in PFC.

The evaluation of S-COMT activity followed by COMT Val¹⁵⁸Met polymorphism studies confirmed that functional (enzyme activity) and genetic results were concordant. In fact, the activity of erythrocyte S-COMT was different depending on the genotype: higher in the Val/Val genotype, followed by the Val/Met genotype, and finally by the Met/Met genotype (Figure 3). As genotype does not change across cells, we can assume that this tendency is similar in the brain. Thus, it seems that incarceration does not induce epigenetic changes since the enzyme activity predicted by the genotype is effectively expressed by the individuals. These data are also in accordance with the literature (Tammimäki & Männistö, 2012; Weinshilboum & Dunnette, 2008).

The distribution of the COMT Val¹⁵⁸Met polymorphism in our sample revealed values higher than those expected for Caucasian individuals regarding the Val/Val genotype, and lower than those expected for the Met/Met genotype (González-Castro *et al.*, 2013). Nevertheless, due to the pattern of conduct, we can assume that our sample population does not represent a general population sample. In previous literature reports, the Val/Val genotype has been associated with the development of ASPD, in adults (Langley *et al.*, 2010). Since ASPD is the only psychiatric disorder associated with premeditated aggression (Frick & White, 2008; Patrick, 2014), the higher prevalence of Val/Val genotype and the clear association of this genotype with premeditated aggression are logical. A possible explanation for these results could be the lower availability of dopamine, at the PFC level caused by Val/Val genotype (Matsumoto *et al.*, 2003; Tunbridge, 2004). Lower availability of dopamine at the prefrontal level seems to be associated with higher ability to change mental representations and higher mental flexibility – yet, lower emotional sensitivity. This biochemical scenario can lead to higher ability to make action plans (Yildirim & Derksen, 2015).

In our study, genotype results were in good agreement with enzyme kinetic assays, in which we have found that higher erythrocyte S-COMT activity was also associated with premeditated aggression. In fact, while the value of K_M was similar in both groups (since it is specific for the enzyme), individuals with premeditated aggression presented a V_{max} value for S-COMT in erythrocytes twofold higher than those of the impulsive group, confirming that individuals with premeditated aggression have more available functional enzyme to convert the substrate (Figure 1).

In individuals with the Met/Met or Val/Met genotype, higher availability of dopamine at the PFC level (Matsumoto *et al.*, 2003; Tunbridge, 2004) was already reported and seems to be associated with higher cognitive stability, less flexibility of mental representations, and higher emotional sensitivity (Yildirim & Derksen, 2015). This can be on the basis of the occurrence of impulsive aggression acts in individuals with lower erythrocyte S-COMT activity.

Although it was neither an objective nor an initial hypothesis, the analysis of our data confirmed previous literature reports in which it is concluded that PCL-R can distinguish between premeditated and impulsive aggression (Blais *et al.*, 2014). In addition, the activity of erythrocyte S-COMT was positively correlated with the PCL-R score (Figure 2). In other words, psychopathic traits measured by PCL-R were positively associated with erythrocyte S-COMT activity. This suggests that COMT activity can interfere with the phenotype of individuals with ASPD and psychopathy (Yildirim & Derksen, 2015). Thus, those who display higher COMT activity may be more emotionally insensitive and more prone to premeditated acts of aggression. Even though the correlation is weak, this biological finding has never been described and can be a starting point for future studies on a novel biological therapeutic target for a population that, so far, did not have relevant pharmacological interventions, besides symptomatic control (Bourne, 2010). Is COMT related to the antisocial personality? Can we interfere in personality through its pharmacological modulation? Although, psychiatrists are still cautious about the possibility of pharmacological or psychotherapeutic intervention in ASPD, this option may constitute a sound scientific basis with possible translation to clinical practice. Other authors have suggested that it is possible to change guilt-driven behaviour through the inhibition of COMT in healthy individuals (Mitchell, Weinstein, Vega, & Kayser, 2018; Sáez, Zhu, Set, Kayser, & Hsu, 2015).

In our sample, the DRD2/ANKK1 TaqIA polymorphism was not associated with different types of aggression. The prevalence of the allele A1 was lower than that described in Caucasian populations (Ma, Wang, Yuan, Su, & Li, 2015). According to previous findings, we expected higher prevalence of the DRD2 allele A1 in our sample, as the sample

consists of offenders with significant substance use disorders (SUD) and psychopathic traits (Ponce *et al.*, 2008; Wu & Barnes, 2013). Nevertheless, in our sample, the presence of DRD2 polymorphism did not seem to be differently associated to aggression types.

The therapeutic approach of aggression has been sustained by antipsychotics and mood stabilisers. However, a recent systematic review (Howner *et al.*, 2020) highlights the lack of knowledge on the effectiveness of pharmacological treatment, within forensic psychiatry. These authors claimed that the frequent use of antipsychotics, sometimes in combination with other pharmacological agents, in this complex and heterogeneous patient group, calls for high-quality studies, in this specific setting. The present study suggests a biological difference in COMT activity between offenders with premeditated aggression and those with impulsive aggression. In fact, blockage of D2 and 5HT2 receptors can be useful for impulsive aggression, yet that is not the case for premeditated acts. Herein, we hypothesise that this type of aggression could be modulated with COMT inhibitors.

Considering the overall characterisation of our sample, we observed that it was mostly composed of individuals who had committed aggressive acts classified as impulsive. This type of aggression distribution is in accordance with that described for forensic populations (Swogger *et al.*, 2015).

The forensic population described here presented an average age, education, and prevalence of violent crimes comparable with other forensic samples (Forrester, Till, Simpson, & Shaw, 2018). From a clinical point of view, we have verified that there was a high prevalence of ASPD and SUD. Other authors had previously reported high prevalence of ASPD and SUD in forensic populations (Widinghoff *et al.*, 2019). The sample was collected from a forensic facility for convicted individuals who had committed multiple and recurrent crimes. This type of population, showing criminal recidivism, has a higher presence of psychopathic traits. In fact, PCL-R high scores, as the ones found in our sample, predict criminal recidivism (Olver & Wong, 2015).

The major limitations of our study are the small sample size, the fact that we have done multiple comparisons between the two groups, and those related to cross sectional studies. This design allowed to compare individuals with premeditated aggression with those with impulsive aggression, at a specific point in time, but we cannot exclude the possibility of low representativeness of the behaviour of the group as a whole (due to the fact that measurements are performed at a specific time point). Considering these limitations, our results are preliminary and shall be confirmed in larger populations. Even though, sample size shall be evaluated considering the particularities of this specific population and the limitations regarding the contact with patients, consultations, and research approval.

In conclusion, in male offenders, impulsive aggression may be associated with lower erythrocyte activity of S-COMT (confirmed by the Val/Val genotype of COMT). This confirms the correlation of COMT with aggression type, but not with its genesis. We believe that our preliminary results constitute a strong basis for future research with implications on the management of impulsive aggression in penitentiary institutions.

Data availability

The original contributions presented in the study are publicly available. This data can be found here: DOI: https://datadryad.org/stash/share/YbGXun9hQD_41NXFTx1MSlciIN3GEVqj4yt9WEu_598.

Author contributions

All authors contributed to the study conception and design.

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Competing interests

The authors have no conflict of interest to declare.

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