Catechol-o-Methyltransferase (COMT), Earlier Abuse, Gene-Environment Interaction in the Prediction of Violence

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Abstract

Several candidate genes have been suggested to play a role in the development of antisocial behavior in association with social and environmental factors. Therefore, the purpose of the present study was to investigate the relationship between the gene Catechol-O-Methyltransferase (COMT) and violence; and to examine whether there were interactions between earlier abuse and COMT in the association of violence. Data were drawn from a Swedish population-based study including 2,500 20-24 year olds. The present study found that depending on which variant of the gene one possess, one will be affected to different degree of adverse environmental factors in association with violence.

Keywords: COMT, exposure to abuse, violent behavior.

Katekol-O-Metyltransferas (COMT), tidigare övergrepp, gen-miljöinteraktion i förutsägelsen för våld

Sammanfattning

Flera kandidatgener har föreslagits spela en roll i utvecklingen av antisociala beteenden i samband med miljöfaktorer. Syftet med den föreliggande studien var därmed att undersöka sambandet mellan genen Katekol-O-Metyltransferas (COMT) och våld; och om det fanns interaktioner mellan exponering för tidigare övergrepp och COMT i samband med senare våld. Data hämtades från en Svensk populationsbaserad studie baserad på 2500 20-24 åringar. Den aktuella studien fann att beroende på vilken variant av genen man besitter, kommer man att påverkas i olika grad av negativa miljöfaktorer såsom försummelse och sexuella övergrepp i samband med våld.

Nyckelord: COMT, misshandel, våldsamt beteende.

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How is one to explain why certain individuals commit violent acts while others abstain even though they have experienced similar adverse events? Previous research shows that children who are exposed to physical abuse or who are victims of neglect are prone to later in life engage in violent behavior (Malinosky-Rummell & Hansen, 1993). About 50 % of those who have been maltreated as children will grow up and engage in criminal behavior, such as violence against others, while the other 50 % will grow up and live a lawful life (Caspi et al., 2002). Furthermore, about 50 % of all crimes are committed by the same individuals within the same family, who only represent 10 % of the community population. This could be explained by adverse environmental factors or by heritable transmissions across family members or by a combination of both (Moffitt, 2005).

An important study that increased the awareness regarding how genetic markers impact the development of different types of antisocial behavior such as violence, attempted to answer the question why some individuals are more affected by negative events than others. This study found that lower activity of monoamine oxidase type A (MAO-A) enzyme associated with vulnerability to abuse as a child significantly increased the risk of developing violent behavior among men (Caspi et al., 2002). The interest in understanding the relationship between genetic markers, environment and violent criminal behavior has existed for a long period of time. The first study to show an association between a genetic marker and violent criminal behavior included men in the same family that exhibited abnormal behavior, such as impulsive aggression and attempted rape. Urine samples found that these men were associated with a total and selective loss of the MAOA-enzyme (Brunner, Nelen, Breakefield, Ropers & Van Oost, 1992). Whereas there is evidence that the MAOA-enzyme interacts with exposure to early abuse and is associated with later antisocial behavior, such as violence (e.g.,

Caspi et al., 2002), no study has yet examined whether a similar relationship can be found for COMT. The purpose of the present study was to investigate the relationship between the enzyme Catechol-O-Methyltransferase (COMT) and violence; and to also examine whether there are interactions between earlier abuse and COMT in the association of violent behavior.

Antisocial and Violent Behavior

Antisocial behavior is considered a broad term and is composed of many constituents but the basic idea is conduct detrimental to other persons or violence where another person's human rights are affected (Tuvblad & Beaver, 2013). To lie and manipulate are examples of destructive behaviors that are included when talking about antisocial behavior, but mostly it is mentioned when the law is violated (Tuvblad & Beaver, 2013). Whereas antisocial behavior is a broad term, violence on the other hand, is defined as behaviors of individuals who intend to try or cause any physical harm to other individuals. This definition involves behaviors such as assault, theft in connection with violence, rape and torture (Reiss & Roth, 1993).

Antisocial behavior is a widespread phenomenon and according to self-reports up to 80 % of all adolescents have engaged in some form of antisocial behavior during their development (Rutter, Giller & Hagell, 1998). Individuals who engage in antisocial behavior, such as violent behavior against others, are not only a burden to their victims, they are also a negative weight for the entire community when it comes to legal action but above all, economic costs in form of the criminal justice system and compensation for victims (Scott, Knapp, Henderson & Maughan, 2001).

In addition to molecular genetic studies, we also know from an abundance of twin and family studies that not only environmental factors are important for an individual's conduct but also heritable influences (Raine, 2008). Regarding heritability of antisocial behavior including violence, research has relied on adoption and twin studies. Meta-analytic reviews regarding genetic studies that attempt to explain antisocial behavior, suggests that

approximately 40 % - 50 % of the variance in antisocial behavior may be explained due to genetic influences (Rhee & Waldman, 2002; Miles & Carey, 1997). While the remaining part of the variance is explained by factors such as the environment around you (Rhee & Waldman, 2002). Children have an increased risk of committing crimes if they have been poorly supervised (Farrington, 1990). Adoption studies have shown that children who already exhibited risk behavior and were later adopted into a family where the legal guardian was previously convicted increased the risk of continued criminal behavior (Cloninger et al., 1982; Mednick et al., 1984).

There are countless environmental risk factors that can tie together victimization and later violent behavior (Widom, 1994). For example, individuals with antisocial behavior such as violent behavior tend to have had antisocial and/or criminal parents (McCord, 1977), grown up in a family with a higher number of children (Fischer, 1984), been raised by parents with poor parental supervision (Smith & Stern, 1997), and have been neglected or abused (Lang, Klinteberg & Alm, 2002). However, it is important to understand how the environment in relation to individual's genetic potential (genotype) contributes to antisocial behavior, such as violence (phenotype) (Groove et al., 1990). Thus, more research is needed regarding determining whether COMT should be interpreted as a risk factor (candidate gene) or as a predictor (Baker, Tuvblad & Raine, 2010), when it comes to antisocial behavior such as violence in association with earlier abuse.

Catechol-o-methyltransferase (COMT)

COMT is an enzyme which is involved in the degradation of catecholamines, which are dopamine, norepinephrine and epinephrine (Pavlov, Chistiakov & Chekhonin, 2012). The COMT gene is situated on chromosome 22q, which conducts a single nucleotide polymorphisms (SNP), encoding for a single amino acid-change in the translated protein. This SNP will result in either a valine (Val) or a methionine (Met) amino acid at the 158^{th} codon

(Lotta et al., 1995). This polymorphism has been identified as a risk factor for various neuropsychiatric disorders, including substance use and addiction, obsessive compulsive disorder and attention deficit hyperactivity disorder (ADHD), to name a few (Hosa'k, 2007). Majority of previous research regarding the COMT gene has focused on individuals with ADHD. Research has shown that individuals with ADHD and carriers of the valine (Val) allele, for example, were more aggressive and had more criminal convictions in comparison with individuals with ADHD possessing the methionine (Met) substitution of COMT (Caspi et al., 2008). However, the link between the COMT gene and various antisocial behaviors has not yet been found in individuals without ADHD (Niv & Baker, 2010).

The COMT enzyme is primarily found in the front parts of the brain as well as areas that handle the regulation of aggressive behavior. Studies have shown that mice lacking the enzyme COMT had higher propensity for aggression, these findings created an interest to investigate whether this link is also seen in humans (Gogos et al., 1998). Today there are several candidate genes which researchers have suggested may play a major role in the development of antisocial behavior, for example the COMT gene (Iofrida, Palumbo & Pellegrini, 2014). Most part of these assumptions regarding candidate genes was distinguished by examining the dopamine system, the serotonin system and the epinephrine/norepinephrine system. As previously mentioned, the COMT gene regulates the degradation of various catecholamines; these in turn control various elements within an individual. For example, the dopamine system is involved in a person's incentive and temperament (Niv & Baker, 2010). Dopamine also works to reduce the effects of serotonin (Fishbein, 2006). The serotonin system is in turn involved in a subject's impulse control, sleep and appetite feelings (Niv & Baker, 2010). Research has shown that the neurotransmitter serotonin also can counteract aggressive behavior (Fishbein, 2006). Last but not least, the epinephrine/norepinephrine-system, which enables fight-or-flight reactions, participates in an individual's autonomic

nervous system (Niv & Baker, 2010).

Further, a key study regarding COMT found that individual characteristics and choice of performance in specific situations can to some extent be explained by the different variants of the COMT gene (Stein, Newman, Savitz & Ramesar, 2006). In other words, it has been shown that individuals differ in various situations depending on whether they possess the COMT gene and valine (Val158 G:G) alleles or the methionine (Met158 A:A) substitution. Individuals behave either after the Warrior Strategy or the Worrier Strategy. Individuals who possess Val158 alleles believe to have an advantage in unpleasant situations (Warrior Strategy), while individuals with Met158 alleles have an advantage when it comes to memory and concentration tasks (Worrier Strategy). Also, in situations where the dopamine level in the body increases (e.g., during stress) individuals with Val158 alleles will have better dopaminergic transmission and better performance, while individuals possessing Met158 alleles on the other hand will have worse performance due to less functional neurotransmission (Stein et al., 2006).

Gene x Environment (GxE) interaction

To date, the vast majority of the GxE studies have been based on the ‘diathesis-stress hypothesis’ (Simons et al.,2012), which suggests that genetic variations (allelic variations in genes) associated with exposure to social adversity will result in behavioral problems. Additionally, the diathesis-stress hypothesis suggest that some individuals, due to their biological, temperamental and/or behavioral characteristics are more vulnerable to the adverse effects of negative experiences, whereas others are relatively resilient with respect to them (Bakermans-Kranenburg & van Ijzendoorn, 2007). Thus, genes that interact with adversity does not confer risk for antisocial behavior, such as violence, but rather alter the susceptibility to the environment (Kim-Cohen et al., 2006). For example, Caspi and colleagues (2002) found that men with alleles of low MAOA activity and who have been victims of

maltreatment, also had issues with antisocial behavior in comparison with men possessing alleles with high activity (Simons et al., 2012). Further, when speaking of Gene x Environment (GxE) interactions, the focus is on different variants of specific genes in individuals that are likely to enhance the risk of problem behaviors (criminal behavior, violence, depression) if the individual is exposed to adverse environments such as abusive parents or neglect (Simons et al., 2011). Instead of talking about these variants of genes as susceptibility genes, they are also referred to as plasticity genes. Plasticity genes are based on the theory that individuals are not only more receptive when it comes to negative environmental experiences, but they are also more responsive when it comes to positive experiences (Belsky et al., 2009). Some individuals are simply programmed to react more vulnerable in certain environmental situations (Belsky, Bakermans-Kraneburg, Marian & IJzendoorn-Marinus, 2007). As an extension of this, the 'differential-susceptibility perspective' put forward that individuals vary in the degree they are affected by experiences or qualities of the environment they are exposed to. Genes are neither inherently good or bad, or even that their behavioral effects depend on person–environment fit, but rather that individuals vary in their plasticity or susceptibility to environmental influences (Pluess & Belsky, 2013). For example, 7-year-old boys with the low-MAOA-activity variant had more mental health problems if they had been victims of abuse, but fewer problems if they had not, compared to boys with the high-MAOA-activity genotype (Kim-Cohen et al., 2006).

The research questions that the present study will attempt to answer are as follows; (1) Is there an association between the COMT gene and violent behavior? (2) Are there any sex differences? (3) Finally, in line with the diathesis-stress theory, we hypothesized that there would be an interaction between COMT and earlier abuse in the association of violent behavior.

Method

Participants

The present study is based on data from a cross-sectional and retrospective population-based Study of Young People's Experiences (RESUMÉ), which is a Swedish study that examines the consequences of various forms of earlier abuse, including physical, sexual and psychological on later outcomes such as criminal, antisocial and aggressive behavior in adulthood, mental and physical health, as well as social adjustment. RESUMÉ consists of 2,500 randomly selected participants (1,314 female participants and 1,186 male participants) born between 1987 and 1991. When the study was conducted, the participants were between 20 and 24 years of age (mean age=22.1, SD=1.4). RESUMÉ is funded by the National Board of Health and Welfare.

Measures

Violence: Violence was measured by 7 items regarding different violent acts (Andershed, Kerr, Stattin, & Levander, 2002). Examples of items were; "Have you participated in fights when out at night?" and "Have you been involved in beating someone so you think or know that he/she needed health care?" The items had 5-point response format running from "No, it has not happened" = 0 to "Yes, more than 10 times" = 5. Responses were summed to create a total violence score indicating severity of violence (Cronbach's Alpha $\alpha = .69$).

Environmental Factors: Exposure to Abuse

Exposure to Physical violence: There were 11 items to measure an individual's exposure to physical violence. Examples of items were; "Has anyone ever chocked you?" and "Has anyone ever hit or beaten you (e.g., at home, in school, or elsewhere?" The items had a 6-point response format from "1 time" = 1, "5 times or more" = 5 and "No" = 6. Responses were summed to create a total physical violence score indicating severity of experiencing

physical violence (Cronbach's Alpha α = .86). Six of these items are from the Juvenile Victimization Questionnaire (JVQ) (Finkelhor, Hamby, Ormrod & Turner, 2005; Hamby, Finkelhor, Ormrod & Turner, 2004). The remaining five items were concluded from other studies to cover different types of physical abuse (Janson, Långberg & Svensson, 2007; May-Chahal & Cawson, 2005).

Exposure to Sexual abuse: There were 7 items to measure an individual's exposure to sexual abuse. Examples of items were; "Has anyone ever touched your private parts when you did not wanted it or forced you to touch theirs or forced you to have (vaginal, oral or anal) sex intercourse?" and "Has anyone ever made you look at their genitals using their physical strength or surprised you, or by exposing themselves to you?" The items were reported in a 6-point response format from "1 time" = 1, "5 times or more" = 5 and "No" = 6. Responses were summed to create a total sexual abuse score indicating the severity of having experienced sexual abuse (Cronbach's Alpha α = .84). Five of these items are from the JVQ (Finkelhor et al., 2005; Hamby et al., 2004). The remaining two items were concluded from the NSPCC study (Chahal & Cawson, 2005).

Exposure to Neglect: There were 5 items concerning neglect. Examples of these items were; "When someone is neglected, it means that the caretakers do not take care of them as they are supposed to do. Maybe enough food was not provided. Growing up, were you neglected?" and "Growing up, did it happen that you had serious troubles, were sad or worried, lacking anyone to help you, listening to you, calming you down and take your concerns seriously and/or protect you against any threats?" The items were reported in a 6-point response format running from "1 time" = 1, "5 times or more" = 5 and "No" = 6. Responses were summed to create a total victim of neglect score indicating the severity of neglect (Cronbach's Alpha α = .77). One of these items are from the JVQ (Finkelhor et al.,

2005; Hamby et al., 2004), the remaining four items were concluded from other studies (e.g., Chahal & Cawson, 2005).

Procedure

Participants were interviewed face-to-face and the interview took about an hour (mean time: 67 minutes), data have also been gathered through self-reports and registers (Miller, Cater, Howell & Graham-Bermann, 2013; Cater, Andershed & Andershed, 2014). DNA saliva samples are available from ~2,000 participants. The participants signed a consent form before the interview started. The participants were given the choice to either answer more sensitive questions on paper or on iPad. Each participant received 400 SEK for their participation and the Ethics Committee at Orebro University authorized the RESUMÉ-study.

Genotyping

DNA was extracted from 200µl of saliva collected with the Oragene self-collection kit (DNA Genotek®) using the silica-based Kleargene DNA extraction method. Genotyping analyses of single nucleotide polymorphisms (SNPs) were performed using the Kbioscience Allele-Specific Polymorphism assay (KASP) based on competitive allele-specific PCR and bi-allelic scoring of the single nucleotide polymorphisms (SNPs). No-template control samples were included to enable the detection of contamination or non-specific amplification. Further, several studies have shown that genomic DNA from saliva and blood samples is comparable in both quantity and quality (Abraham, Maranian & Spiteri, 2012) and saliva samples have previously been used when examining genes for antisocial behavior (Burt & Mikolajewski, 2008).

Statistical Analysis

T-test was performed to determine sex differences in participants' victimization and participants' violence against others. Regarding COMT, to determine the distribution of the

different variants of the COMT gene between the sexes, a Chi^2-test was performed. Mean (M) define the average value in a sample while standard deviation (SD) is an approximation of the typical variance (spread), around the mean (Field, 2009). Main and interaction effects of genetic and environmental factors were analyzed by general linear models (GLM) in SPSS. A p-value < .05 was considered significant for interactions and main effects (Fleiss, 1986). Furthermore, to determine the direction (positive or negative) of the significant two-way interactions, regressions models were performed (not shown). All analyzes is performed in the Statistical Package for Social Science 21.0 (SPSS).

Results

Table 1 shows sex differences in participants' victimization of physical violence, sexual abuse and neglect, also the participants' violence against others. The distribution of the different variants of the COMT gene between the sexes is also presented.

Males to a greater extent than females have been exposed to physical violence ($t_{(1782)} = 9.57$, $p < .001$). Females, however, have to a greater extent been exposed to sexual abuse ($t_{(1782)} = 12.63$, $p < .001$) and neglect ($t_{(1782)} = -3.32$, $p < .01$). Males reported having committed more violent acts ($t_{(1782)} = 7.22$, $p < .001$) towards others compared to females. No significant relationships between different variants of the COMT gene and sex were found.

Table 1
Sex differences in participants' victimization, violence against others and distribution of COMT.

	Males	Females		
	n (%)	*n (%)*		
	M (SD)	*M (SD)*	*t*	*Sig.*
Participant victimization				
Physical violence	571 (68)	451 (48)	9.57	.001***
	2.45 (2.17)	1.51 (1.97)		
Sexual abuse	65 (7.7)	313 (33.2)	12.63	.001***
	0.15 (0.63)	0.89 (1.59)		
Neglect	72 (8.6)	124 (13.1)	-3.32	.010**
	0.09 (0.28)	0.13 (0.34)		
Violence against others	152 (18.1)	61 (6.4)	7.22	.000***
	1.09 (0.27)	1.02 (0.09)		
COMT			Chi^2	
A:A	273 (32.5)	307 (32.6)	.85	.654
G:A	413 (49.2)	448 (47.5)		
G:G	154 (18.3)	188 (19.9)		

Note. *n* = number of participants; *%* = percent; *M* = mean value; *SD* = standard deviation; *Chi²* = Chi-square value; t = t-test-value. A:A = Met:Met; G:A = Val:Met; G:G =Val:Val. *** *p* <.001; ** *p* <.01

The results from the General Linear Model (GLM) are presented in Table 2. The GLM regression analysis showed significant associations. Violence was separately significantly associated with COMT ($F_{(4)} = 7.105$, $p < .001$) and sex ($F_{(1)} = 8.858$, $p < .001$). Violence was significantly associated with three 2-way interactions of COMT x Neglect ($F_{(8)} = 3.459$, $p <. 001$), COMT x Sexual Abuse ($F_{(10)} = 3.109$, $p < .001$) and COMT x SEX ($F_{(4)} = 6.792$, $p < .001$). Also, violence was significantly associated with three 3-way interactions of COMT x Neglect x SEX ($F_{(5)} = 4.558$, $p < .001$), COMT x Sexual Abuse x SEX ($F_{(10)} = 2.261$, $p < .001$), and Neglect x Sexual Abuse x SEX ($F_{(3)} = 7.407$, $p < .001$).

Next, to determine the direction (positive or negative) of the significant 2-way interactions, regression models were performed. Those exposed to higher levels of neglect ($B = 0.041$, $p > .397$) or sexual abuse ($B = 0.022$, $p > .608$) were to a greater extent carriers of the valine (Val158 G:G) alleles in association with violent behavior. Females were to a larger extent than males carriers of the methionine (Met158 A:A) substitution of COMT ($B = 0.008$, $p > .645$).

Table 2
Results of General Linear Model of Genetic Factors and Environmental Risk Factors Associated with Violent Behavior.

Violent behavior	GLM		
	df	*F*	*p*
1. COMT	4	7.105	.001***
2. Victim of Physical violence	3	.490	.689
3. Victim of Neglect	3	1.154	.326
4. Victim of Sexual abuse	3	1.636	n.s.
5. Participants SEX	1	8.858	.003***
COMT x Physical violence	12	.212	n.s.
COMT x Neglect	8	3.459	.001***
COMT x Sexual abuse	10	3.109	.001***
COMT x SEX	4	6.792	.001***
Physical violence x Neglect	5	1.116	n.s.
Physical violence x Sexual abuse	7	.641	n.s.
Physical violence x SEX	3	.537	n.s.
Neglect x Sexual Abuse	4	5.718	.001***
Neglect x SEX	3	1.337	n.s.
Sexual abuse x SEX	3	1.026	n.s.
COMT x Physical violence x Neglect	10	.227	n.s.
COMT x Physical violence x SEX	12	.282	n.s.
COMT x Physical violence x Sexual abuse	26	.311	n.s.
COMT x Neglect x SEX	5	4.558	.001***
COMT x Neglect x Sexual abuse	12	1.329	n.s.
COMT x Sexual abuse x SEX	10	2.261	.013**
Physical violence x Neglect x Sexual abuse	10	.736	n.s.
Physical violence x Neglect x SEX	3	.088	n.s.
Physical violence x Sexual abuse x SEX	7	.433	n.s.
Neglect x Sexual abuse x SEX	3	7.407	.001***
R Squared = .200 (Adj. R^2 = .132)			

Note. df = degrees of freedom; *F* = F-value; n.s = not significant
*** p <.001; ** p <.01

In summary, the GLM regression analysis showed that the participants in the present study showed different levels of violence depending on which variant of the COMT gene they possess. Levels of violence were also depended on the participants' sex.

Discussion

How is one to explain why certain individuals commit violent acts while others abstain even though they have experienced similar adverse events? An individuals' genetic potential and the environment in relation to antisocial behavior such as violence, has long been of interest, but there are additional knowledge gaps that need to be pursued. This is the first Swedish study to examine whether the COMT gene is associated with violent behavior in interaction with earlier environmental exposure to physical violence, sexual abuse and neglect.

The results of this study showed that depending on which variation of the gene COMT an individual possesses, this will affect how an individual reacts to adverse events; it will also have an impact on how an individual copes with certain situations. *The 'diathesis-stress hypothesis'* (Simons et al., 2012), which is based on the idea that individuals genetic variations (A:A, G:A, G:G) in association with exposure to social adversity (sexual abuse and neglect) will partly explain why some individuals engage in problem behaviors (violence against others). In line with this, the present study showed that individuals were more vulnerable towards negative environmental factors, in this case sexual abuse and neglect, if they were carriers of the valine (Val158 G:G) alleles, in that they showed higher levels of violence compared to individuals possessing the methionine (Met158 A:A) alleles. Henceforth, *the 'diathesis-stress hypothesis'* also suggests that some individuals have a greater resistance when it comes to negative experiences depending on which genetic variation they possess (Bakermans-Kranenburg & van Ijzendoorn, 2007). The present study are in line with this also in that individuals with the methionine (Met158 A:A) alleles were not equally susceptible to sexual abuse and neglect in association with violence compared to individuals possessing the valine (Val158 G:G) substitution. In other words, levels of violence differed between individuals possessing different COMT-alleles.

Additionally, the present study showed that females to a greater extent than males were carriers of the methionine (Met158 A:A) alleles and females also reported being exposed to sexual abuse and neglect to a greater extent compared to males. Also, males reported committing more violent acts toward others compared to females. Once again, in connection with *the 'diathesis-stress hypothesis'*, some individuals are more vulnerable to the adverse effects of negative experiences, whereas others are relatively resilient with respect to them depending on their biological and temperamental characteristics (Bakermans-Kranenburg & van Ijzendoorn, 2007). Could the present studys aforementioned results regarding sex differences, in some extent be explained by their genetic characteristics regarding COMT? The present study's finding in relation to this hypothesis, indicate that females are more resistant to negative experiences (sexual abuse and neglect) due to their genetic characteristics (Met158 A:A), indicating that females higher levels of exposure to earlier abuse did not contribute to higher levels of violent behavior toward others. Similarly, the male participants violence against others could to some part be due to their genetic variation (Val158 G:G) of COMT, indicating that males lower levels of exposure to earlier abuse did contribute to higher levels of violent behavior toward others.

Furthermore, the present study found that depending on which variant of the COMT gene that an individual possesses, either A:A (Met:Met), G:A (Val:Met) or G:G (Val:Val), the individual will be affected to different degrees of adverse experiences such as neglect and sexual abuse. As a result, an individual who possesses the G:G variant of the COMT gene and becomes a victim of either neglect and/or sexual abuse will react based on the *Warrior Strategy* and pursue the most violent behavior in comparison with individuals who have experienced exactly the same type of abuse but which possess another variant of the gene. Individuals carrying the valine alleles (G:G) and react in unpleasant situations through the *Warrior Strategy* will have better performance during stress, due to better dopaminergic

transmission, in other words pursue more violent behaviors. Meanwhile, individuals carrying the methionine alleles (A:A) and react through the *Worrier Strategy* will be more successful in situations that require good memory, but during stressful situations these individuals will have poorer performance due to less functional dopaminergic transmission (Stein, 2006), pursue less violent behaviors compared to valine carriers. These results are in line with previous research showing that individuals differ in various situations depending on whether they possess the COMT gene and valine (Val158 G:G) alleles or the methionine (Met158 A:A) substitution (Stein, 2006).

Additionally, three 3-way interactions were also significantly associated with violence: The first one between COMT, neglect and sex. The second one between COMT, sexual abuse and sex and the last significant three-way interaction was between neglect, sexual abuse and sex. As previously mentioned, it is difficult to interpret the results from 3-way interactions, therefore no further analysis were conducted, leaving it to future research. However, these results may be due to the fact that all the aforementioned variables (COMT, SEX, COMT x Neglect and COMT x Sexual Abuse) were significant regarding either main effects or on 2-way interaction level and that this affects the level of significance on the 3-way interaction level as well.

An unexpected finding was that exposure to physical violence did not predict later violence toward others. There may be several reasons for this unexpected finding. First of all, individuals who become victims of violence, for example, will not always exhibit criminal behavior themselves, nor become violent individuals (Caspi et al., 2002). Henceforth, the present study did not control for current living conditions, working situation and family status, which are all factors that can affect an individual's legitimate behavior (Moffitt, 1993). Nor did the present study investigate the role of protective environmental factors that may be important to an individual's previous exposure and subsequent non-existent problem

behavior.

Previous research has shown an association between earlier abuse, including physical violence, sexual abuse and neglect and later problem behavior such as alcohol use, depression, violence and criminal behavior, to name a few (Gilbert et al., 2008). Importantly, the present study provides new knowledge to the field on the mechanism behind the association between exposure to earlier abuse and violent behavior by showing that this relationship is partly explained by COMT and its variation of alleles. Future studies should therefore examine the relationships among COMT, various risks, but most importantly include protective factors in order to determine if COMT can be considered as a plasticity gene. In other words, determine if different variants of the COMT gene alleles contributes to individuals becoming more susceptible to environmental influences. Additional, examine whether different variants of the COMT gene alleles or only the COMT gene per se has an impact when it comes to individuals becoming more affected by negative events and also, more susceptible towards positive events.

Conclusion

Depending on which variation of the gene COMT an individual possesses, this will affect how an individual reacts to adverse events, it will also have an impact on how an individual copes with certain situations. These important findings provide new knowledge about the interaction between genes and environmental factors and their relationship to various problem behaviors, in this case violence against others. Further, it is important to keep in mind that molecular and behavior genetic studies do not seek to justify an individual's criminal actions and to find reasons for removing individual responsibility and their own choice of actions. Rather, the main focus is to expand our knowledge on the relationships among genes, environmental exposures and behavioral problems to further our understanding

regarding the mechanisms behind these associations. To better understand these underlying mechanism is a first step towards more successful intervention strategies.

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