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COMT but not serotonin-related genes modulates the influence of childhood abuse on anger traits

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Abstract

Anger-related traits are regulated by genes as well as early environmental factors. Both childhood maltreatment and genes underlie vulnerability to suicidal behaviors, possibly by affecting the constitution of intermediate phenotypes such as anger traits. The aim of this study was to test the interaction between nine candidate genes and childhood maltreatment in modulating anger-related traits in 875 adult suicide attempters. The State-Trait Anger Expression Inventory and the Childhood Trauma Questionnaire were used to examine anger traits and traumatic childhood experiences respectively. The functional polymorphism of the catecholamine-O-methyl-transferase (COMT) gene Val158Met significantly modulated the association between sexual abuse and anger-trait level ($p=0.001$). In the presence of sexual abuse, individuals carrying the Val high-activity allele displayed greater disposition towards anger than individuals homozygous for the Met allele ($p=0.0003$). Notably, none of the serotonin-related genes influenced the effect of childhood abuse on anger traits. The results of the present study suggest that anger-trait level is influenced by the interaction between childhood abuse and functional polymorphism in the COMT gene. This study was carried out in a population with a high frequency of childhood abuse and a high disposition towards anger, and replication in healthy subjects is needed.

Introduction

Anger is a basic, commonly experienced emotional state that consists of feelings of variable intensity, from mild irritation to intense fury and rage. Anger has been related to several phenomena in medicine and several behavioral and psychiatric conditions (Chida & Steptoe, 2009, Lara & Akiskal, 2006). A high level of anger traits has indeed been associated with eating disorders (Fassino *et al.*, 2001), borderline personality disorder (Zanarini *et al.*, 2004), drug addiction (De Moja & Spielberger, 1997), and suicidal behaviors (Baud, 2005, Baud *et al.*, 2007). For the latter, in comparison to controls suicide attempters have indeed been shown to express higher level of anger (Baud, 2005, Baud *et al.*, 2007).

Anger is part of the brain's fight-or-flight response to a perceived threat. This multi-dimensional structure is composed of physiological, behavioral and cognitive aspects that have been shown to correlate positively with aggression, hostility and impulsivity (Ramirez & Andreu, 2006). From this perspective, particular attention has been paid to anger in the field of suicidal behaviors. Indeed, subjects with a history of suicide attempts have been shown to display a greater tendency towards anger or greater difficulty in outwardly expressing anger than control (Baud, 2005, Baud *et al.*, 2007).

Knowledge of the sources of individual differences in anger remains sparse but includes genetic and environmental factors. Twin and family studies have indeed suggested that anger-related traits are inheritable (Rebollo & Boomsma, 2006, Sluyter *et al.*, 2000). Several genes involved in serotoninergic and catecholaminergic neurotransmissions have recently been associated with anger traits and/or related measures of anger such as aggression or impulsivity, including tryptophan hydroxylase 1 (*TPH1*) (Baud *et al.*, 2009, Manuck *et al.*, 1999, Rujescu *et al.*, 2002), several serotonin receptors (*5-HTR*) (Giegling *et al.*, 2006, Serretti *et al.*, 2007, Zouk *et al.*, 2007), the monoamine oxidase A (*MAOA*) (Alia-Klein *et al.*, 2008, Manuck *et al.*, 2000) and the catecholamine O-methyl transferase (*COMT*) genes (Alia-

Klein *et al.*, 2008, Baud *et al.*, 2007, Baud *et al.*, 2009, Giegling *et al.*, 2006, Manuck *et al.*, 1999, Rujescu *et al.*, 2002, Serretti *et al.*, 2007, Zouk *et al.*, 2007)

Environmental factors such as childhood maltreatment, lack of social support and negative life events were also found to predict high levels of anger (Springer *et al.*, 2007). Finally, the effects of gene–environment interaction (GxE) on measures of anger are also taken into account although this area has not been thoroughly investigated to date. Exactly how GxE modulates anger related traits is not yet understood. Some studies such as those published by Caspi *et al.* (Caspi *et al.*, 2002) provide some preliminary evidence pointing to the interaction of *MAOA* and early maltreatment on aggression and anti-social personality traits.

In this study, we intend to explore the extent to which some GxE underlies inter-individual differences in the expression of anger in a population of suicide attempters. In view of the importance of childhood maltreatment in the development of suicidal behaviors (Dube *et al.*, 2001), the close relationship between suicidal behaviors and anger (Horesh *et al.*, 1997) and the existence of a genetic component in suicidal behaviors (Bellivier *et al.*, 2004), a population composed of suicide attempters is ideal to unravel the environmental and genetic components of anger-related traits.

Materials and Methods

Subjects

Suicide attempters (N=875) were included after informed written consent was obtained. Suicide attempters were recruited from consecutive admissions to the psychiatric units of three university hospitals – Montpellier and Créteil (France), and Geneva (Switzerland) – between 1994 and 2006. Suicide attempt was defined as the occurrence of self-harming acts with an intent to end one's own life (Mann, 2003). Suicide attempters were all of European ancestry for at least two generations. Suicide attempters were assessed for psychiatric diagnoses using either the French version of the Diagnostic Interview for Genetics Studies (DIGS) or the Mini International Neuropsychiatric Interview (MINI) (Nurnberger *et al.*, 1994, Preisig *et al.*, 1999, Sheehan *et al.*, 1998). The study protocol was approved by research ethics committees in each centre.

Behavioural and Childhood trauma assessments

Anger-related traits were assessed with the State-Trait Anger Expression Inventory (STAXI) (Spielberger, 1988). The STAXI is a 44-item self-report questionnaire measuring the experience and expression of anger in accordance with the state-trait personality theory (Norlander & Eckhardt, 2005). The experience of anger comprises State Anger (the current feelings experienced by an individual) and Trait Anger (individual disposition to experience anger or the ease, frequency and intensity of becoming angered), whereas the expression of anger comprises the three components of Anger-In (which measures the individual tendency to suppress angry feelings), Anger-Out (the tendency to outwardly express anger towards people or objects) and Anger control (the capacity of an individual to regulate or control his/her anger).

The Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) is a retrospective self-report questionnaire that examines the traumatic childhood experiences of

adults and adolescents. It assesses five types of childhood trauma: emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse. CTQ has demonstrated excellent test-retest reliability and convergent validity (Bernstein *et al.*, 1994). It comprises 28 items and each item is rated from 1 (never) to 5 (very often). Scores range from 5 to 25 for each type of abuse. According to Bernstein and Fink, thresholds or cut scores have been set for each type of trauma at four levels of maltreatment: None, Low, Moderate and Severe (see Table 1 for cut-off scores for each of the five CTQ subscales). The different cut-offs have been shown to have good specificity and sensitivity (Bernstein & Fink, 1998).

Genotyping

The following polymorphisms previously associated with related measures of anger were chosen for the analyses: the *TPH1* rs1800532 (A218C) polymorphism (Jollant *et al.*, 2007, Manuck *et al.*, 1999, Rujescu *et al.*, 2002); the *MAOA* variable number of tandem repeat polymorphisms in the promoter region (MAOA-u-VNTR) (Jollant *et al.*, 2007, Shih & Chen, 1999); the functional rs6295 (C-1019G) promoter polymorphism in the *5-HTR1A* gene (Keltikangas-Jarvinen *et al.*, 2008, Serretti *et al.*, 2007); the *5-HTR2A* rs6311 (A-1438G) and rs6313 (C102T) polymorphisms (Keltikangas-Jarvinen *et al.*, 2008, Turecki *et al.*, 1999); the *5-HTR1B* promoter rs130058 (A-161T) and rs6296 (G861C) polymorphisms (Zouk *et al.*, 2007); and *COMT* rs4680 (Val158Met) polymorphism (Rujescu *et al.*, 2003) and with suicidal behaviors: three *TPH2* polymorphisms: rs11179000 and rs11179001 in the intron 4 and rs7305115 in exon 7 (Jollant *et al.*, 2007); the 44 base pair insertion/deletion polymorphism within the serotonin transporter gene (5-HTTLPR) (Jollant *et al.*, 2007, Roy *et al.*, 2007); and the Brain Derived Neurotrophic (*BDNF*) rs6265 (Val66Met) polymorphism (Perroud *et al.*, 2008). All primers and genotyping conditions were carried out as previously

published (Baud *et al.*, 2007, Etain *et al.*, 2004, Jollant *et al.*, 2007, Paoloni-Giacobino *et al.*, 2000, Perroud *et al.*, 2008) or are available upon request.

Statistical analyses

Demographic and clinical characteristics of the study population were described using mean and standard deviation for quantitative variables and proportions for categorical variables. We used a linear regression model to test for the main effect of genes. P-values were two-tailed, and $p< 0.05$ was considered to indicate statistical significance. The statistical package STATA V.10 and PLINK software (Purcell *et al.*, 2007) were used for the analyses.

For statistical purposes and to enhance the power of tests, all cases of childhood trauma were pooled in two categories: not-abused or not-neglected versus abused or neglected individuals (by pooling low, moderate and severe abused/neglected subjects) (Perroud *et al.*, 2008). Sex, age at interview, diagnosis, and the recruitment centre were added as confounding variables because there were significant associations for each of these variables with at least one of the STAXI subscales, the childhood trauma items and/or the genetic polymorphisms. When a significant main effect for a genetic polymorphism was detected on a STAXI sub-score, we tested for an interaction between polymorphism and childhood maltreatment on this STAXI sub-scale.

The one-sample Kolmogornov-Smirnov test was used to investigate whether STAXI sub-scale distributions were normally distributed. The Trait Anger scale was normally distributed and therefore used without any transformation in our analyses. As regards other subscales, since no transformation was able to normalize them, we firstly used the robust command (provided with STATA) in order to take into account skewed distributions. Secondly we used a permutation test that randomly assigned STAXI sub-scales to subjects whilst keeping each subject's genotype and environmental variable fixed. These permutation

procedures have been shown to relax assumptions about the normality of continuous phenotypes and to be robust against abnormal distribution patterns (Epstein & Satten, 2003, Purcell *et al.*, 2007, Zhao *et al.*, 2000). For each analysis, the empirical *p* value was based on 10 000 permutations. Results were then compared to those obtained with the original distribution in order to verify the accuracy of our model.

In a second step and if an interaction was observed for a polymorphism, we tested for a possible evocative correlation association (evocative rGE) by determining with a chi-square test if the genetic polymorphism could be involved in evoking or eliciting maltreatment exposure. If so, we used logistic regression to adjust on sex, age at interview, recruitment centre and diagnosis.

Since we compared genotypic and allelic distributions of 13 polymorphic markers between non-maltreated and maltreated individuals on five STAXI sub-scales, a correction for multiple testing was required. It is difficult to correct for multiple testing in a multi-stage analysis. The primary purpose of our research was to detect interactions between the STAXI anger sub-scales and the childhood abuse and neglect measures in association with the genetic polymorphisms tested. We initially tested for the main effects of association with the five STAXI sub-scales. For genetic variants with a liberal p-value threshold of p=0.05, we then proceeded to test for interaction with the five childhood trauma items. We used a more stringent p-value threshold for the interactions. We tested 9 independent polymorphisms (since there is strong linkage disequilibrium (LD) between the polymorphisms within *TPH2, 5-HRT2A*, and *5-HTR1B*); the childhood trauma items are all highly correlated, and we therefore consider this to be equivalent to two independent measures. For a Bonferroni correction on the p-values for interaction, we therefore used p=0.05/(9*2) = 0.0028 as a threshold for significance.

Power calculation

Power analysis was performed using the QUANTO program (Gauderman & Morrison, 2006). We aimed to detect genetic effects accounting for at least 2% of variance in the various STAXI sub-scales under a dominant genetic model for a polymorphism with a minor allele frequency of 0.2. The power for detecting such an effect was calculated for the nominal significance level $\alpha = 0.05$. The sample of 875 individuals had 0.99 power to detect an effect of a genetic marker accounting for 2% of the variance for the studied trait at an α level of 0.05.

Assuming that 40% of the subjects are exposed to childhood maltreatment and that the latter accounts for at least 1% of the variance of the trait, the GxE analysis had a power of 0.88 to detect an interaction effect accounting for more than 3% of the variance at an α level of 0.0028. In short, our study is sufficiently powered to detect not only the clinically significant effects of genes on STAXI sub-scales but also GxE.

Results

Genotype and allele frequencies of genetic polymorphisms in suicide attempters were in Hardy-Weinberg equilibrium and similar to the frequencies reported in other clinical samples (Table 2) (Roy *et al.*, 2007, Rujescu *et al.*, 2002, Rujescu *et al.*, 2003, Serretti *et al.*, 2007, Spurlock *et al.*, 1998, Thorisson *et al.*, 2005, Zalsman *et al.*, 2005, Zouk *et al.*, 2007).

Table 1 displays the demographic and clinical characteristics and rates of childhood abuse and neglect in suicide attempters. Most of the suicide attempters suffered from major depressive disorder (68.8%), were female (70.7%), and displayed non-violent suicide attempt (75.4%). The majority of suicide attempters revealed that they had suffered from childhood abuse of at least minor severity: 38.2% of suicide attempters reported a history of physical abuse, 39.9% sexual abuse, 51.1% physical neglect, 67.9% emotional abuse and 84.7% emotional neglect. Women scored significantly higher on the Trait Anger sub-scale (24.5 [6.1] vs. 23.4 [5.8]; b=0.89; t=2.02; 95%CI from 0.01 to 1.79; p=0.044) and lower on the Anger Control sub-scale (21 [4.7] vs. 21.8 [4.4]; b=-0.76; t=-2.22; 95%CI from -1.42 to -0.09; p=0.027) than men. Moreover, age was negatively correlated to Trait Anger and Anger Out scores (b=-0.05; t=-3.26; 95%CI from -0.08 to -0.02; p=0.001 and b=-0.05; t=-4.13; 95%CI from -0.07 to -0.02; p<0.0001 respectively).

There were more females (N=471, 73.8%) in Montpellier than in Creteil (N=70, 61.4%) and Geneva (N=78, 63.4%) (X2=10.9; df=2; p=0.004). Moreover subjects recruited in Geneva scored significantly higher on Anger Control subscale than individuals from Creteil (21.8 [5.0] vs 20.5 [4.7]; b=1.33; t=2.17; 95%CI from 0.12 to 2.53; p=0.031). For these reasons, recruitment centre was added as confounding variable in all the analyses. No other variables distinguished individuals from the different center of recruitment.

Effect of childhood abuse on anger traits

Results of the regression analyses estimating the effect of childhood trauma on STAXI sub-scales are shown in Table 3. Interestingly, neither sexual abuse nor emotional neglect had an effect on any of the STAXI sub-scales. However, other forms of maltreatment had a principal effect on most of the different STAXI sub-scales (Table 3).

Effects of genotypes and GxE on anger traits

COMT Val158Met

As previously described (Baud *et al.*, 2007), we found that *COMT* Val158Met had a principal effect on the Trait Anger sub-scale. Individuals carrying the high activity Val allele scored significantly higher on the Trait Anger scale than individuals homozygous for the low activity Met allele (Val/Val=24.9 [5.6]; Val/Met=24.1 [6.2]; Met/Met=23.4 [6.1]), (b=-0.85; t=-2.96; 95%CI from -1.35 to -0.19; p=0.003) (Table 4).

On the same lines, we also noted that *COMT* Val158Met had a main effect on Anger Out scores, (Val/Val=17 [4.8]; Val/Met=16.8 [5.1]; Met/Met=16 [4.7]), (b=-0.48; t=-2.05; 95%CI from -0.98 to -0.03; p=0.041) (Table 4). *COMT* genotypes did not affect other STAXI sub-scales.

We found a significant interaction between *COMT* Val158Met and sexual abuse on Trait Anger ($F_{(2,762)}$=6.96; p=0.001) (Figure 1). This interaction was highly significant when looking at individuals with a Met/Met genotype compared to those carrying a Val allele ($F_{(1,764)}$=13.13; p=0.0003). This result was significant even after correction for multiple testing. In patients reporting sexual abuse, this interaction was explained by a significantly lower Trait Anger score among individuals carrying a Met/Met genotype (22.3 [5.7]) compared to carriers of a Val allele (ValVal (25.9 [6.1]) or ValMet (25.4 [6.3]) (b=-3.75; t=-3.79; 95%CI from -5.70 to -1.81; p<0.0001 and b=-3.61; t=-4.00; 95%CI from -5.38 to -1.83; p<0.0001). We also found a significant three-way interaction with sex ($F_{(5,757)}$=2.81; p=0.016)

showing that the above interaction was mainly explained by the female population of suicide attempters (Figure 2).

To less of an extent but along the same lines as the results obtained for Trait Anger, *COMT* Val158Met also interacted with sexual abuse when considering Anger Out scores ($F_{(2,760)}$=3.38; p=0.035). However, this interaction was no longer significant following adjustment for multiple testing.

We did not observe any interaction between other types of maltreatment and *COMT* Val158Met for Trait Anger and Anger Out.

TPH1 A218C

THP1 A218C was found to have a main effect on Anger Control scores (Table 3). Subjects carrying the AA genotype displayed lower Anger Control scores than the AC and CC carriers (20.3 [4.4] vs. 21.5 [4.4] and 21.3 [4.9] respectively; b=0.51; t=2.19; 95%CI from 0.14 to 2.00; p=0.029) (see Table 4). Other STAXI sub-scales were not influenced by *THP1* A218C.

There was no significant interaction between childhood maltreatment and TPH1 A218C polymorphism on the Anger Control sub-scale.

MAOA u-VNTR

MAOA u-VNTR was found to have a significant effect on the Anger State STAXI sub-scale among male suicide attempters. Individuals carrying the H allele scored significantly higher on this sub-scale (b=1.89; t=2.05; 95%CI from 0.05 to 4.11; p=0.041) (Table 4). An interaction between *MAOA* u-VNTR and sexual abuse on Anger State scores was observed but did not survive correction for multiple testing (data not shown).

5-HTR1B A-161T, *5-HTR1B* G861C, *5-HTR2A* A-1438G, *5-HTR2A* C102T, *TPH2* rs11179000, *TPH2* rs11179001, *TPH2* rs7305115, *5-HTR1A*, *BDNF Val66Met* and *5-HTTLPR*

These polymorphisms were not found to have any principal effect on STAXI scores.

rGE

Finally we tested for a possible evocative genotype-environment correlation (evocative rGE) between *COMT* Val158Met and sexual abuse. No evocative rGE was found.

Discussion

We found that *COMT* Val158Met polymorphism modulates the association between childhood sexual abuse and adulthood anger-trait level. In the presence of sexual abuse, individuals carrying the Val allele display a higher disposition towards anger than individuals homozygous for the Met allele. Our results corroborate the findings of three recent investigations analyzing the modulating effect of *COMT* Val158Met on different outcomes. Savitz *et al.* (Savitz *et al.*, 2008) found that Val/Val genotype, and not Met/Met genotype, was associated with increasing levels of dissociation in subjects exposed to higher levels of childhood trauma. Thapar *et al.* (Thapar *et al.*, 2005) found that Val/Val genotypes are particularly susceptible to the effects of lower birth weight in developing anti-social behavior. And finally Stefanis *et al*. (Stefanis *et al.*, 2007) showed that carriers of the Val allele were more sensitive to the effect of stress on the development of psychosis than those with the Met/Met genotype. Overall, these findings support the involvement of *COMT* Val158Met in mediating the relationship between early traumas and psychopathology during adulthood with the Val allele being more sensitive to environmental influences.

The current findings partly contrast with those from other studies showing increased sensitivity to stress in carriers of the Met as opposed to the Val allele (Drabant *et al.*, 2006, Smolka *et al.*, 2005). Moreover, as the Met allele has been associated with violent suicide attempts and a greater tendency towards external expression of anger (Rujescu *et al.*, 2003), one would have expected to find this allele associated with a high level of anger. The results of direct association studies between *COMT* Val158Met and psychiatric disorders have been inconsistent with some involving the Met allele (Park *et al.*, 2002, Rujescu *et al.*, 2003) and others the Val allele (Glatt *et al.*, 2003, Wonodi *et al.*, 2003). Val158Met polymorphism certainly appears to have a pleiotropic effect on human behavior and various cognitive functions (Mier *et al.*, 2009). Partly for this reason, several recent studies have focused on

GxE rather than the principal genotypic effect. Although contrasting evidences have emerged from these findings, most of the interactions (ours included) conducted with this polymorphism provided evidence of synergism between the Val allele and environmental exposure (Caspi *et al.*, 2005, Henquet *et al.*, 2006). It can be assumed that both the Val and Met alleles are involved in the development of psychopathology through different interactions with specific environmental factors but with more environmental susceptibility in Val carriers.

The inconsistencies in studies analyzing the effect of Val158Met polymorphism have been the subject of many debates. Some authors proposed that *COMT* Val158Met may modulate the balance of tonic and phasic dopamine function in different areas of the brain depending on specific environment (Bilder *et al.*, 2004). According to this hypothesis, the Val allele is associated with decreased tonic dopamine but increased phasic dopamine neurotransmission subcortically. The predominance of phasic over tonic dopamine in Val allele carriers may explain reduced stability of neural networks but an increase in cognitive flexibility. The opposite effect is put forward for the Met allele (Nolan *et al.*, 2004, Rosa *et al.*, 2004). From this perspective, the Val allele, which is associated with increased COMT activity (Shield *et al.*, 2004), may result in reduced dopamine neurotransmission in the prefrontal cortex associated with deficits in working memory, attention and executive functioning (Bilder *et al.*, 2004, Goldberg *et al.*, 2003). Our finding confirms the hypothesis that lower levels of tonic dopamine, associated with the Val high activity allele, have less control over phasic (subcortical) dopamine release resulting in an abnormally high phasic dopamine response in the nucleus accumbens (Bilder *et al.*, 2004, Meyer-Lindenberg *et al.*, 2005). It is therefore tempting to presume that, with equal environmental exposure, stress-induced phasic dopamine release will be greater in Val allele carriers than in Met/Met individuals. This would also explain why most of the interactions found the Val allele to be

associated with vulnerability to psychopathologies when exposed to adverse environmental conditions.

An inverted 'U'-shape relationship between dopamine levels and prefrontal cortex function could provide another related explanation for the paradoxical findings (Mattay *et al.*, 2003). In this model it is postulated that both excessive and insufficient dopamine levels impair working memory performance and that only a narrow range of dopamine levels offer optimal functioning. The pleiotropic effect of Val158Met polymorphism could be explained by the position of each allele on this particular 'U'-shaped curve where the Val/Val genotype is positioned in a less favorable position compared to the Met allele carriers (Meyer-Lindenberg & Weinberger, 2006, Mier *et al.*, 2009).

In Goldman's 'warrior/worrier' model (Goldman *et al.*, 2005), each allele is supposed to be maintained in the population because each confers an environmental-specific advantage. In Goldman's view, the Val allele is useful in threatening environments where maximal performance is required despite threat and pain (a warrior strategy), whereas the Met allele may be useful in complex environments where maximal performance is required in terms of memory and attention tasks (a worrier strategy). The high level of anger observed in Val allele carriers sexually abused in childhood could be the surviving response of this warrior strategy to this particularly threatening environment.

Val158Met polymorphism is not the only variation in the *COMT* gene. Considerable complexity in haplotypes and LD patterns exist across this gene and vary among populations around the world (Mukherjee *et al.*, 2008). Inconsistencies regarding association studies may be due to the haplotypic combination of alleles comprising the Val158Met and several other SNPs across the gene. Several studies also revealed that sub-stratification in the investigated population could also be responsible for discrepancies between studies (Bray *et al.*, 2003, Mukherjee *et al.*, 2008). Given the recent investigations showing moderate stratification in

even closely related populations, this hypothesis is not to be ruled out (Novembre *et al.*, 2008).

Finally and as evidenced in our previous finding (Baud *et al.*, 2007), the moderating effects of the *COMT* Val158Met may be sex-specific. We have also highlighted that the observed interaction was present only in the female sample, which corroborates the idea of the sex-specificity of this polymorphism. This could also partly explain the discrepancies noted in studies concerning Val158Met polymorphism.

Limitations

The measurement of childhood maltreatment was retrospective – hence recall bias may have influenced the reports. Sample size is another issue in GXE studies (Hunter, 2005). In the present study, the power was enhanced by the accurate measurement of the phenotype and childhood maltreatment and the fact that we explored biologically plausible candidates. Moreover, our study is sufficiently powerful to detect such an interaction. Another limitation is that we only considered SNPs that reached a specific level of significance for the interaction analyses, excluding potential significant interactions.

COMT Val158Met does not account for all the genetic variation in the COMT activity (Nackley *et al.*, 2006) and, future studies genotyping further SNPs within the gene could help to disentangle the complex relationship between COMT gene and outcome. We however did not genotype other SNPs in this gene and were therefore not able to perform such analysis.

Although the direct association between COMT Val158Met and Anger Trait was significant, this association was not as strong as in our previous article (Baud *et al.*, 2007). Indeed, when looking only at the new sample of suicide attempters (448 subjects), the results were not significant. In the present study, the two samples were pooled as there was no

heterogeneity between them. However, in both samples, the interaction was significant and in the same direction. This suggests that it is crucial to take into account environmental factors to consistently detect a significant association.

Interestingly, sexual abuse did not significantly influence Anger dimensions on itself. One explanation for this intriguing result could be that we are looking at an enriched population for history of childhood sexual abuse and anger related traits and therefore at the right end of the distribution for both variables. It could be therefore more difficult to highlight a potential association. The other possible explanation is that the retrospective investigation of sexual abuse could have increased either false positives or false negatives and secondarily led to a loss of significant association.

Conclusions

To the best of our knowledge, this is the first study showing an interaction between *COMT* Val158Met polymorphism and childhood sexual abuse in modulating anger-trait levels in adulthood. These are important findings as they point towards sexual abuse as main environmental factors over other types of maltreatment, interacting with susceptibility genes. Recent studies suggest that the early environment acts through epigenetic modifications in order to modify behavior (Mcgowan *et al.*, 2009, Weaver *et al.*, 2004). It could be hypothesized that early and repeated exposure to adverse environmental factors may elicit permanent changes in gene expression patterns via epigenetic modifications. From this perspective, Val allele carriers could be more susceptible to these epigenetic modifications, which would explain why most of the studies found this allele to be associated with increased psychopathology when exposed to an adverse environment.

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Figure Legends

Figure 1: Trait Anger scores by sexual abuse and COMT Val158Met polymorphism in 822 suicide attempters (Ns: Val/Val=159, Val/Met=228, Met/Met=106 for individuals without history of sexual abuse; Ns: Val/Val=93, Val/Met=159, Met/Met=77 for individuals with history of sexual abuse).

Figure 2: Trait Anger scores by sexual abuse and COMT Val158Met polymorphism for males (N=239; Val/Val=67, Val/Met=74, Met/Met=34 for males without history of sexual abuse; Val/Val=11, Val/Met=38, Met/Met=15 for males with history of sexual abuse) and females (N=583; Val/Val=92, Val/Met=154, Met/Met=72 for females without history of sexual abuse; Val/Val=82, Val/Met=121, Met/Met=62 for females with history of sexual abuse) respectively

Tables

Table 1: Clinical and demographic characteristics of the 875 suicide attempters

Table 1	Clinical and demographic characteristics of the 875 suicide attempters		
		N	%
Sex	Male	256	29.3
	Female	619	70.7
Recruitment centre	Montpellier	638	72.9
	Geneva	123	14.1
	Paris	114	13.3
Diagnoses	Major depressive disorder	602	68.8
	Bipolar disorder	186	21.3
	Schizophrenia and related disorders	24	2.7
	Anxiety disorders	33	3.8
	Alcohol/Cocaine/Heroin dependence	8	0.9
	Unknown	19	2.2
	No psychiatric disorder	3	0.3
Emotional neglect	Yes	741	84.7
	Low (10 to 14)	*275*	*31.4*
	Moderate(15 to 17)	*159*	*18.2*
	Severe (18 to 25)	*307*	*35.1*
	No	134	15.3
Emotional abuse	Yes	594	67.9
	Low (9 to 12)	*182*	*20.8*
	Moderate (13 to 15)	*121*	*13.8*
	Severe (16 to 25)	*291*	*33.7*
	No	281	31.1
Physical neglect	Yes	447	51.1
	Low (8 to 9)	*178*	*20.3*
	Moderate (10 to 12)	*136*	*15.5*
	Severe (13 to 25)	*133*	*15.2*
	No	428	48.9
Physical abuse	Yes	334	38.2
	Low (8 to 9)	*105*	*12*
	Moderate (10 to 12)	*81*	*9.3*
	Severe (13 to 25)	*148*	*16.9*
	No	541	61.8
Sexual abuse	Yes	349	39.9
	Low (6 to 7)	*68*	*7.8*
	Moderate (8 to 12)	*117*	*13.4*
	Severe (13 to 25)	*164*	*18.7*
	No	526	60.1
		Mean	SD
Age		39.6	12.9
STAXI	State Anger	20.9	7.6
	Trait Anger	24.1	6
	Anger In	21.3	5
	Anger Out	16.6	4.9
	Anger Control	21.2	4.6

Table 2: Genotypes in all suicide attempters

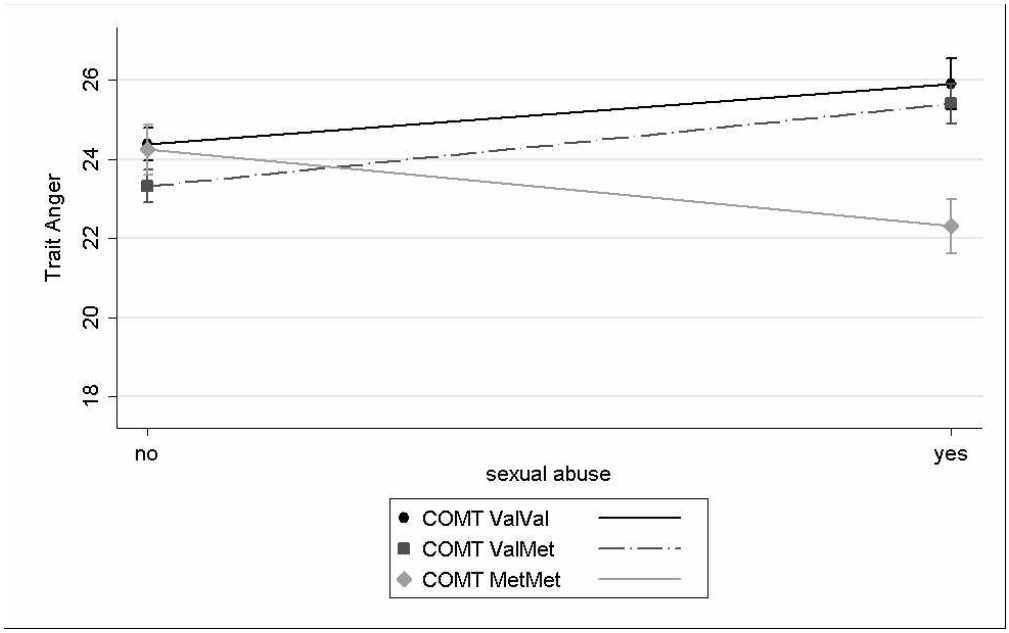
Table 2		Genotypes in all suicide attempters					
		N	%			N	%
COMT Val158Met	**ValVal**	252	30.66	*5-HTR1A C-1019G*	**CC**	209	25.61
	ValMet	387	47.08		**CG**	430	52.7
	MetMet	183	22.26		**GG**	177	21.69
5HTTLPR	**LL**	266	32.56	*5-HRT2A A-1438G*	**AA**	125	23.11
	LS	399	48.84		**AG**	267	49.35
	SS	152	18.6		**GG**	149	27.54
TPH1 rs1800532	**AA**	152	18.51	*5-HRT2A C102T*	**CC**	57	25.91
	AC	393	47.87		**CT**	118	53.64
	CC	276	33.62		**TT**	45	20.45
TPH2 rs11179000	**AA**	517	63.05	*5-HRT1B A-161T*	**AA**	400	48.9
	AT	259	31.59		**AT**	331	40.46
	TT	44	5.37		**TT**	87	10.64
TPH2 rs11179001	**AA**	10	1.22	*5-HT1B C861G*	**CC**	49	5.98
	AG	89	10.84		**CG**	321	39.19
	GG	722	87.94		**GG**	449	54.82
TPH2 rs7305115	**AA**	124	15.14	*MAOA u-VNTR male*	**L**	82	34.6
	AG	398	48.6		**H**	155	65.4
	GG	297	36.26				
BDNF Val66Met	**MetMet**	41	4.98	*MAOA u-VNTR female*	**LL**	70	12.05
	ValMet	270	32.81		**LH**	237	40.79
	ValVal	512	62.21		**HH**	274	47.16

Table 3: STAXI by childhood trauma

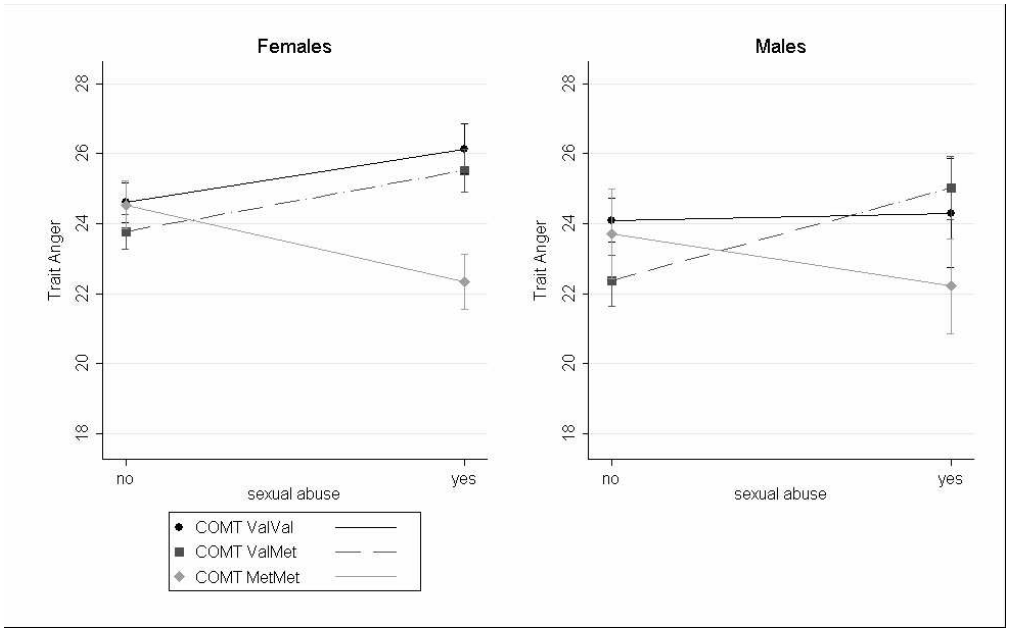
Table 3		STAXI by childhood trauma					
	Variable	**Mean**	**Std. Dev.**	**Mean**	**Std. Dev.**	**b; t; (95%CI)**	**p**
		no		**yes**			
Sexual abuse	State anger	20.61	*7.59*	21.43	*7.62*	*0.59; 1.05; (-0.51 to1.68)*	0.295
	Trait anger	23.76	*5.95*	24.76	*6.13*	*0.76; 1.73; (-0.1 to 1.61)*	0.083
	Anger in	20.92	*4.84*	21.76	*5.25*	*0.72; 0.37; (-0.01 to 1.44)*	0.052
	Anger out	16.39	*4.84*	17.02	*5.03*	*0.43; 1.20; (-0.27 to 1.13)*	0.232
	Anger control	21.12	*4.51*	21.21	*4.8*	*0.19, 0.56; (-0.48 to 0.85)*	0.578
		no		**yes**			
Emotional neglect	State anger	20.31	*8.21*	21.09	*7.52*	*0.76; 1.05; (-0.66 to 2.19)*	0.295
	Trait anger	23.75	*5.96*	24.24	*6.06*	*0.39; 0.70; (-0.72 to 1.51)*	0.484
	Anger in	21.07	*5.31*	21.29	*4.96*	*0.24; 0.50; (-0.70 to 1.18)*	0.617
	Anger out	16.43	*5.35*	16.69	*4.84*	*0.17; 0.36; (-0.74 to 1.07)*	0.718
	Anger control	21.75	*4.57*	21.04	*4.63*	*-0.63; -1.43; (-1.49 to0.23)*	0.152
		no		**yes**			
Emotional abuse	State anger	19.83	*7.36*	21.5	*7.7*	*1.44; 2.51; (0.32 to 2.58)*	0.012
	Trait anger	23.03	*5.7*	24.7	*6.13*	*1.43; 3.19; (0.55 to 2.31)*	0.001
	Anger in	20.38	*5.1*	21.68	*4.93*	*1.23; 3.27; (0.49 to 1.98)*	0.001
	Anger out	15.79	*4.64*	17.06	*5.01*	*1.12; 3.08; (0.41 to 1.84)*	0.002
	Anger control	21.29	*4.33*	21.09	*4.76*	*-0.15; -0.44; (-0.84 to 0.53)*	0.657
		no		**yes**			
Physical neglect	State anger	20.19	*7.42*	21.71	*7.76*	*1.52; 2.87; (0.48 to 2.57)*	0.004
	Trait anger	23.78	*5.62*	24.53	*6.41*	*0.82; 1.98; (0.01 to 1.64)*	0.048
	Anger in	20.79	*5.09*	21.71	*4.9*	*0.95; 2.72; (0.27 to 1.64)*	0.007
	Anger out	16.35	*4.69*	16.94	*5.13*	*0.70; 2.05; (0.03 to 1.36)*	0.041
	Anger control	21.6	*4.6*	20.71	*4.61*	*-0.91; -2.86; (-1.55 to -0.29)*	0.004
		no		**yes**			
Physical abuse	State anger	20.54	*7.65*	21.65	*7.56*	*0.88; 1.59; (-0.21 to 1.96)*	0.112
	Trait anger	23.74	*5.74*	24.86	*6.46*	*0.95; 2.20; (0.11 to 1.80)*	0.028
	Anger in	20.94	*4.92*	21.78	*5.13*	*0.80; 2.10; (0.05 to 1.47)*	0.037
	Anger out	16.09	*4.65*	17.57	*5.22*	*1.35; 3.88; (0.67 to 2.03)*	0.0001
	Anger control	21.27	*4.47*	20.94	*4.85*	*-0.24; -0.72; (-0.89 to 0.41)*	0.471

Table 4: Significant associations between SNPs and STAXI sub-scales

Table 4	Significant associations between SNPs and STAXI sub-scales			
		N	mean (SD)	b; t; adjusted p for allele comparisons
			Trait Anger	
COMT Val158Met	ValVal	240	24.9 (5.6)	-0.85; -2.96; 0.003
	ValMet	368	24.1 (6.2)	
	MetMet	171	23.4 (6.1)	
			Anger Out	
	ValVal	239	17 (4.8)	-0.48; -2.05; 0.041
	ValMet	367	16.8 (5.1)	
	MetMet	171	16 (4.7)	
			Anger Control	
TPH1 A218C	AA	144	20.3 (4.4)	0.51; 2.19; 0.029
	AC	369	21.5 (4.4)	
	CC	265	21.3 (4.9)	
			State Anger	
MAOA uVNTR male	L	78	18.9 (6.1)	1.89; 2.05, 0.041
	H	150	21 (7.4)	



345x215mm (72 x 72 DPI)



345x215mm (72 x 72 DPI)