Interaction between BDNF Val66Met and childhood trauma on adult’s violent suicide attempt.

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Abstract

Genetic factors, specially those related to serotoninergic activities, and childhood maltreatment have both been implicated in suicidal behaviour (SB). However, little attention has been paid to the possible interaction between genes and childhood maltreatment in the comprehension of SB.

Brain derived neurotrophic factor (BDNF) plays an important role in the growth of serotoninergic neurons during childhood and therefore represents a good candidate for studies on SB. Moreover, decreased levels of BDNF have been found in the prefrontal cortex of suicide victims. In our study we wanted to see if Val66Met (a BDNF functional single nucleotide polymorphism) could moderate the effect of childhood maltreatment on the onset, number and violence of SB in a sample of 813 Caucasian suicide attempters.

Childhood maltreatment was evaluated using the Childhood Trauma Questionnaire (CTQ). We used a regression framework to test the interaction between Val66Met and childhood maltreatment.

Childhood sexual abuse was associated with violent suicide attempts in adulthood only among Val/Val individuals and not among Val/Met or Met/Met individuals (p=0.05). The severity of childhood maltreatment was significantly associated with a higher number of suicide attempts and with a younger age at onset of suicide attempt.

This result suggests that Val66Met modulates the effect of childhood sexual abuse on the violence of SB. It is proposed that childhood sexual abuse elicits brain structural modifications through BDNF dysfunction and enhances the risk of violent SB in adulthood.
In suicidal behaviour (SB), little attention has been paid to the possible interplay of genes with environmental factors such as life events and social support. Most genetic studies assumed a direct path from gene to disease, but this approach has not proven to be effective for complex psychiatric disorders such as SB. Recently, research has paid attention to the gene-environment interaction (GxE) as a new and different comprehensive model of psychiatric disorders (Caspi & Moffitt, 2006; Hunter, 2005; Lesch, 2004; Moffitt et al. 2005). Developmental adversities are known risk factors for SB in adulthood; childhood sexual and physical abuse, disturbed relationship with parents and parental mental illness are all known risk factors for SB (Agerbo et al. 2002; Beautrais et al. 1996; Brent et al. 2002; Brodsky et al. 2001; Dube et al. 2001; Fergusson et al. 2000; Johnson et al. 2002; Mann et al. 2005; McHolm et al. 2003; Molnar et al. 2001; Romans et al, 1995). Moreover, a graded relationship between the number of childhood maltreatments and risk of suicide attempts (SA) throughout the life span has been reported (Dube et al. 2001; Ullman & Brecklin, 2002). These findings and those of other family studies (Brodsky et al. 2001; Mann et al. 2005) suggest that stressful life events such as childhood maltreatment influence the onset, number, violence and course of SB (Beautrais et al. 1996; Brent et al. 2002; Dube et al. 2001; Roy, 2004; Roy & Janal, 2005; Ullman & Brecklin, 2002).

Stressful childhood events could modify children’s brain development in order to confer a vulnerability to SB that will be expressed in adulthood. Such stressful situations have been linked to abnormalities of serotonin (5-HT) systems in animal and human studies (Barr et al. 2003; Bennett et al. 2002; Hariri et al. 2002). Animal studies have shown that maltreatment stress early in life alters 5-HT neurotransmitters in ways that can persist into adulthood and can influence aggressive behaviour (Barr et al. 2003; Bennett et al. 2002). Therefore, genes
involved in both 5-HT transmission and brain neurodevelopment are major candidates for vulnerability to SB. Among 5-HT related genes, several studies provided significant evidence supporting the association between the 5-HT transporter (5-HTT) gene and SB and/or violent SB (Anguelova et al. 2003; Bellivier et al. 2004; Bondy et al. 2003; Courtet et al. 2005; Li & He, 2007; Lin & Tsai, 2004; Rujescu et al. 2003).

Brain derived neurotrophic factor (BDNF) plays an important role in the regulation and growth of 5-HT neurons during childhood (Altar et al. 1994; Altar et al. 1997, Mamounas et al. 1995; Siuciak et al. 1996). Acute and chronic stress has been reported to inhibit hippocampal BDNF synthesis (Murakami et al. 2005; Pizarro et al. 2004; Scaccianoce et al. 2003) and the protein has been shown to play an important role in mediating neural plasticity in response to adverse social experiences (Berton et al. 2006; Tsankova et al. 2006). The 5-HT dysfunction found in SB could, therefore, be the expression of low level of BDNF, which impeded the normal development of 5-HT neurons during brain development. This hypothesis is supported by two recent studies that found a decreased level of BDNF in the hippocampus and prefrontal cortex of suicide victims (Dwidedi et al. 2003; Karege et al. 2005). Recently, it has been shown that cerebrospinal fluid level of BDNF was significantly lower in atopic dermatitis patients with SA compared to those without SA (Kimata, 2005). Moreover, plasma levels of BDNF have been shown to be significantly lower in suicidal depressive patients than non-suicidal ones (Kim et al. 2007).

BDNF G196A (Val66Met or rs6265) is a functional single nucleotide polymorphism (SNP) which results in a valine (Val) to methionine (Met) change at position 66. It is located in the 5′ pro-BDNF sequence (Egan et al. 2003). Egan et al. (2003) demonstrated in vitro that BDNF secretion was reduced in 66Met BDNF neurons compared with 66Val neurons. Although most studies did not provide evidence for an association between Val66Met and SB (Hong et al. 2003; Hwang et al. 2006), recently Iga et al. (2007) found the 66Met allele to be associated
with SB in a Japanese population of depressive subjects. However, none of these studies examined specific phenotypes of suicide attempters in a Caucasian sample and no one took environmental factors into account. In our study, we wanted to see if interaction between Val66Met and childhood maltreatment could moderate the onset, number and violence of SB among a sample of Caucasian suicide attempters.

Methods

Subjects

Suicide attempters (N=813) were included after informed written consent was obtained. The study was approved by the ethical committees of the university of Geneva (Switzerland), Montpellier and Créteil (France). Suicide attempters were recruited from consecutive admissions to the psychiatric unit of three university hospitals – Geneva (Switzerland), Montpellier and Créteil (France) - between 1994 and 2006. SA was defined as the occurrence of self-directed injurious acts with intent to end one's own life (Mann, 2003). Suicide attempters were all Caucasians for at least two generations. They were interviewed by trained psychiatrists or psychologists, 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).

Suicide attempters were classified as violent or non-violent according to the criteria proposed by Asberg et al (1976). Hanging attempts, use of firearms or knives, throwing oneself under a train and jumping from heights were all considered to be violent attempts; drug intake and superficial wrist cutting were considered to be non-violent SA.

Age at onset of SA was defined as the age at which the patient first committed a SA. Age at onset was assessed by the interviewer and then blindly rated by an independent psychiatrist.
according to medical case notes and DIGS or MINI. As for lifetime diagnosis, the number of SA was estimated by means of a final best-estimate process using the DIGS or MINI and medical records and, when available, information from relatives.

Childhood abuse

The Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) is a retrospective self-report questionnaire that examines the traumatic experiences during childhood and adolescence. 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; Bernstein & Fink, 1998; Bernstein et al. 1997; Fink et al. 1995). 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 trauma. 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. The different cut-offs have been shown to have good specificity and sensibility (Bernstein & Fink, 1998).

Genotyping

Genomic DNA was isolated from peripheral lymphocytes by standard salting-out procedures. Val66Met polymorphism was genotyped by polymerase chain reaction (PCR) followed by restriction enzyme digestion. A 113 bp segment was amplified by PCR, using the following primers: F 5’-GAGGCTTGACATCATTGGCT-3’ and R 5’-CGTGTACAAAGTCTGCCGTCCT-3’ and Hybaid thermocycler. Target sequences were amplified in a 25 μl reaction solution containing 100 ng genomic DNA, 1U Taq polymerase (Eurobio, Brunschwig, Basel,
Switzerland), 1.5 mM MgCl$_2$, 100 nmol dNTP and 10 pmol of each primer. Thirty cycles were performed, each consisting of 94°C for 30 s, 54 °C for 30 s, and 72°C for 30 s. Samples were then digested overnight with 4 U of Eco72I (MBI Fermentas). The fragments were separated on a 10% polyacrylamide gel at 250 V and then visualized with ethidium bromide. The uncut product size was 113 bp (allele A). Allele G comprised the cut bands of 78 and 35 bp. DNAs from three subjects with AA, AG and GG genotypes which have been confirmed by nucleotidic sequencing were used as controls in all the series of PCR-digestion.

Statistical analyses

Demographic and clinical characteristics of the population were described by using mean and standard deviation for quantitative variables and proportions for categorical ones. Chi-square tests and t-tests were used to compare the suicide attempters groups (violent and non-violent). We used a logistic regression model, with gender, recruitment centre, Axis I diagnoses and number of SA as covariates to test the interaction between Val66Met and childhood maltreatment on the violence of SA. We first compared abused (by pooling low, moderate and severe abused subjects) versus non-abused individuals. In order to exclude the maximum number of false positives and to enhance the power of the tests, we chose, in a second regression analysis, to compare only severely abused with non-abused individuals. Gender, Axis I diagnoses, recruitment centre and number of SA were added as confounding variables, because there was a significant association for each of these variables between violent and non-violent suicide attempters (see table 1). To test the significance of the interaction, we used the Wald chi-square test.

A linear regression was also used to analyse the interaction between childhood maltreatment and Val66Met on age at first SA with adjustment for sex, diagnoses, recruitment centre and
severity of SA. As the distribution of the number of SA was skewed, we categorized the variable in two categories (cut-off based on the 75 percentile: 1 to 3 versus more SA). We then used a logistic regression with adjustment for the same variables as for the linear regression.

In a second step, we tested for a possible evocative correlation association (evocative rGE) by investigating whether Val66Met could be involved in evoking or eliciting maltreatment exposure. We first used a simple chi-square test and then a multinomial regression to analyse the association between Val66Met and the likelihood of exposure to maltreatment. The multinomial regression was used to estimate the odds ratio (OR) that low, moderate or high severity of abuse, compared with no abuse, was associated with a particular genotype. Multinomial regression was used because it enabled mildly, moderately or severely abused individuals to be compared with non-abused subjects in the same model for each CTQ subscale, while adjusting for confounding variables such as sex and age in an initial analysis. In a second analysis, we also adjusted for diagnoses, recruitment centre and for severity, age at onset and number of SA. The coefficients were represented as the odds ratio (OR) and 95% confidence intervals (95%CI). We used statistical package Stata V.8.

Results

Genotype and allele frequencies of Val66Met were in Hardy-Weinberg equilibrium (X2=0.16, p=0.92). Moreover genotype and alleles frequencies were similar to those reported in another Caucasian population (Met/Met: 4.9% (N=40), Val/Met: 33% (N=268), Val/Val: 62.1% (N=505) and Met: 21.4%; Val: 78.6%; X2=3.47; p=0.18 and X2=0.06; p=0.8 for genotype and allele comparisons respectively) (Neves-Pereira et al. 2005).
When compared with non-violent suicide attempters, violent suicide attempters were significantly more likely to be male and had a significantly higher number of past SA (table 1). Table 2 displays rates of childhood abuse and neglect in the different groups of suicide attempters. The majority of suicide attempters revealed they suffered from a childhood abuse of at least low severity. 69.5% of suicide attempters experienced emotional abuse, 84.7% emotional neglect, 38.7% physical abuse, 49.1% physical neglect and 40.5% sexual abuse. There was no significant difference in the frequency of the severity of different childhood maltreatments. Genotype frequency of Val66Met was not associated with either violent SA or non-violent SA, suggesting that Val66Met does not influence the severity of SB, at least when assessed by the lethality of the means used (table 2).

Results of logistic regression analyses estimating the association between sexual abuse (no vs. yes) and percentage of violent SA as a function of Val66Met genotype are shown in figure 1 and table 2. The main effect of Val66Met (adjusted for other variables) was not significant (b=-0.004, SE=0.18, z=-0.02, p=0.98), whereas the main effect of sexual abuse (adjusted for other variables, comprising Axis I disorders) was significant (b=0.45, SE=0.18, z=2.49, p=0.013) suggesting that environment influences the severity of SB. The results also revealed a significant interaction between Val66Met and sexual abuse (X²=3.8; df=1; p=0.05). This interaction was highly significant when considering severe sexual abuse versus none (X²=4.74; df=1; p=0.029). The interaction also showed that childhood sexual abuse was associated with adult violent SA only among individuals carrying the Val/Val genotype (b=0.65, SE=0.22, z=2.93, p=0.003) but not among individuals carrying a Met allele (Val/Met or Met/Met genotypes) (b=-.019, SE=0.34, z=-0.06, p=0.956).

We did not find any interaction between Val66Met genotype and severity of sexual abuse, emotional abuse, emotional neglect, physical neglect or physical abuse and age at onset and number of SA. However, the severity of each of the childhood maltreatments, with the
exception of physical neglect, were significantly associated with a higher number and a younger age at onset of SA (see table 3).

Age at onset and number of SA were not influenced by Val66Met genotype (table 3).

Even though there was no significant association between the severity of each scale of the CTQ and the two genotype groups in a chi-square test (emotional neglect: X²=2.6 p=0.45, emotional abuse: X²=3.5 p=0.3, physical neglect: X²=2.5 p=0.47, physical abuse: X²=3.4 p=0.33, sexual abuse: X²=5.2 p=0.016), the multinomial analysis showed a significant difference between the two genotype groups in the severity of sexual abuse (p=0.037 when comparing severe to none) they experienced, suggesting that genotype influences exposure to childhood maltreatment and the existence, therefore, of a possible evocative genotype-environment correlation (evocative rGE). Individuals homozygous for the Val allele in comparison to those carrying the Met allele reported significantly more severe sexual abuse than no sexual abuse (table 4).

Discussion

We found that BDNF Val66Met moderates the effect of childhood maltreatment on the violence of SA. Frequency of violent SA was higher in individuals reporting severe sexual abuse and carrying the Val/Val genotype than in individuals in the same group carrying a Met allele, even after adjusting for gender, recruitment centre, number of SA and Axis I diagnoses. In other words, Val/Val genotype seemed to be associated with violent gesture among suicide attempters who had suffered from severe sexual abuse. This is, to our knowledge, the first study to demonstrate such an interaction. Among the different childhood maltreatments, history of childhood sexual abuse has been the most strongly linked to SB (Brent et al. 1999; Brown et al. 1999; Fergusson et al. 1996; Gladstone et al. 1999; Gladstone et al. 2004;
Kaplan et al. 1997; Nelson et al. 2002; Romans et al. 1995) as well as with guilt, self-blame and hopelessness, which are themselves linked to SB (Martin et al. 2004; Harrington et al. 2006). Our results emphasize the importance of the severity of the abuse for violent SB. A severe, chronic or cumulative exposure to sexual abuse could, therefore, elicit brain structural modifications through BDNF dysfunction and enhance violent SB in adulthood. BDNF has been shown to play an important role in the regulation and growth of 5-HT neurons (Altar et al. 1994; Altar et al. 1997; Gaspar et al. 2003; Lyons et al. 1999; Mamounas et al. 1995; Siuciak et al. 1996). In BDNF-mutant mice, the physiology and structure of central 5-HT neurons were disturbed, as were the behaviour linked to 5-HT dysfunction, including increased aggressiveness, which, in turn, has been linked to SB (Lyons et al. 1999).

Several association studies in psychiatric research have examined the Val66Met variant. Given the lower depolarization-induced secretion of BDNF when the Met allele is present (Egan et al. 2003), an association between a psychiatric disorder and Met allele would normally be expected (Dwidedi et al. 2003; Karege et al. 2005; Kim et al. 2007; Kimata, 2005). However, to date, results have proved to be conflicting. If, on the one hand, the Val allele seems to confer genetic risk for some psychiatric diseases such as bipolar disorder, on the other, in the case of other psychiatric disorders, the Met allele seems to be the variant at risk (Gratacos et al. 2007; Neves-Pereira et al. 2002). Val66Met does not affect the mature BDNF protein function, but has been shown to alter the pro-BDNF and, thus, to affect the regulated secretion of the mature peptide (Chen et al. 2004; Egan et al. 2003). To date, we do not know what the different BDNF levels are in humans with respect to the different possible genotypes (Val/Val; Val/Met and Met/Met). Moreover, there could be differential regional BDNF secretion according to the different genotypes in the human brain, which could explain the discrepancies between studies. As shown by our study, environmental factors should also be taken into account not only in order to find a positive association but also to highlight
which allele is a possible risk factor according to the given environmental exposure. In this perspective, our study strongly suggests that sexual abuse and, more generally, other environmental factors should be taken into account in the future, not only in order to find positive associations but also to define better complex or discrepant associations such as those found for BDNF Val66Met and psychiatric disorders. Thus, without the GxE approach, previous gene-association studies of Val66Met and SB could have been negative in error (Caspi & Moffitt, 2006; Hunter, 2005).

Limitations

One limitation of our study could be its retrospective design. It is very difficult to obtain precise and reliable measures of environmental exposure, particularly if the exposure typically occurs over extended periods of life. The potential for poor recall (misclassification) of past exposure in both cases and controls might attenuate the estimated risk. Another bias of retrospective design (case-control study) is selection bias. If the race or ethnicity of the controls is substantially different from that of the cases, then spurious associations with gene variants that differ by race or ethnicity (that is, population stratification) will occur. This hypothesis would suggest that our violent suicide attempters were from a different ethnicity than our non-violent suicide attempters, which does not seem to be the case, as all subjects were recruited in the same way. Finally, because genetic factors partially mediate the individual’s recall of their environment, CTQ could be contaminated by genetic effects (Plomin & Bergeman, 1991).

Gene-environment correlation

In GxE studies, unidentified genetic influence should be excluded and it should be verified that the association between the environmental risk factor and the disorder is not mediated by an unknown third variable (Jaffee & Pice, 2007; Moffitt et al. 2005). Indeed, the association between childhood maltreatment and SB might be explained by two different kinds of
genotype-environment correlation (rGE). Firstly, parents might transmit to their children both an adverse rearing environment and a genetic susceptibility toward developing SB (passive rGE). Secondly, a child may, by his behaviour, elicit harsh treatment by adults because of a particular genotype (evocative or active rGE). Even though we were not able to exclude passive rGE (no available data), we investigated a possible evocative rGE in our study. We found that individuals with Val/Val genotype compared to those with Val/Met or Met/Met genotype reported severe sexual abuse more frequently than no abuse. These results suggest an evocative rGE and raise the difficult question as to whether among Val/Val individuals brain structure modifications precede and/or enhance severe sexual abuse, which is secondarily associated with violent SB. This hypothesis should be treated with caution, firstly because the test we used (multinomial regression) for the analyses of rGE is more accurate (increased risk of type 1 error) than a simple chi-square association test, which was not significant in our study. The second reason is the above-mentioned recall bias or misclassification. This bias could be enhanced by the results of a recent study which suggested that the low-activity Met allele interacts with sexual abuse scores to result in reduced memory test performance (Savitz et al. 2007). From this perspective, Met carriers may report less sexual abuse than Val homozygous individuals because of poor memory only. Finally, as mentioned above, we did not exclude a passive rGE. Suggesting an evocative rGE, especially in the context of sexual abuse, is a delicate finding and all affirmation of it should be confirmed more than once before any comments or conclusions. Our results should therefore be replicated in order to confirm either the GxE or the evocative rGE we found.

Conclusion

In conclusion, our results suggest that subjects with childhood sexual abuse constitute a unique subgroup at high risk of violent SA, especially for individuals carrying the BDNF Val/Val genotype. If these results were to be confirmed, this subgroup would require
specialized treatment and integrative approaches, not only to facilitate the evocation of the abuse and the resolution of guilt, self-blame and isolation, which are linked to subsequent distress in adults (Lange et al. 1999), but also to prevent further SAs. Unresolved early trauma may further complicate recovery and lead to the recurrence of SA and death. Moreover, the identification of childhood sexual abuse and other childhood maltreatment in patients who present with psychiatric disorder or SA is important, because we found that a history of sexual abuse and childhood maltreatment is likely to play a key role in not only the severity of SB (for sexual abuse) but also in both onset and recurrence of SA.
References


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### Table 1: Clinical and demographic characteristics of suicide attempters, violent and non-violent suicide attempters

<table>
<thead>
<tr>
<th></th>
<th>Suicide attempters (N=813)</th>
<th>Non-violent suicide attempters (N=615)</th>
<th>Violent suicide attempters (N=198)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Age at interview</strong></td>
<td>39.8 (12.9)</td>
<td>39.45 (13.2)</td>
<td>40.7 (11.7)</td>
<td>0.225</td>
</tr>
<tr>
<td><strong>Age of first suicide attempt</strong></td>
<td>31.26 (13.5)</td>
<td>31.7 (13.6)</td>
<td>29.8 (13.1)</td>
<td>0.085</td>
</tr>
<tr>
<td><strong>Number of suicide attempts</strong></td>
<td>3.13 (4.3)</td>
<td>2.7 (2.9)</td>
<td>4.5 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>228 (28.04)</td>
<td>142 (23)</td>
<td>86 (43.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>585 (71.96)</td>
<td>473 (77)</td>
<td>112 (56.6)</td>
<td></td>
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<tr>
<td><strong>Diagnoses</strong></td>
<td></td>
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<tr>
<td><strong>Bipolar disorder</strong></td>
<td>174 (21.4)</td>
<td>127 (20.7)</td>
<td>47 (23.7)</td>
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<tr>
<td><strong>Major depressive disorder</strong></td>
<td>581 (71.46)</td>
<td>456 (74.2)</td>
<td>125 (63.1)</td>
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<tr>
<td><strong>None</strong></td>
<td>43 (5.29)</td>
<td>28 (4.6)</td>
<td>15 (7.6)</td>
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<tr>
<td><strong>Schizophrenia and related psychotic disorders</strong></td>
<td>15 (1.85)</td>
<td>4 (26.7)</td>
<td>11 (5.6)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Recruitment centre</strong></td>
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<tr>
<td><strong>Creteil</strong></td>
<td>53 (6.52)</td>
<td>29 (4.72)</td>
<td>24 (12.12)</td>
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<tr>
<td><strong>Montpellier</strong></td>
<td>659 (81.06)</td>
<td>521 (84.72)</td>
<td>138 (69.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Geneva</strong></td>
<td>101 (12.42)</td>
<td>65 (10.57)</td>
<td>36 (18.18)</td>
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Table 2 Childhood maltreatments among violent and non-violent suicide attempters

<table>
<thead>
<tr>
<th></th>
<th>Non-violent suicide attempters (N=615)</th>
<th>Violent suicide attempters (N=198)</th>
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<tr>
<td></td>
<td>N (%)</td>
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- **Emotional abuse**
  - None: 180 (30.6) vs. 58 (30.2)
  - Low: 134 (22.8) vs. 34 (17.7)
  - Moderate: 72 (12.2) vs. 35 (18.2)
  - Severe: 202 (34.4) vs. 65 (33.9)
  - None: 91 (15.6) vs. 28 (14.3)
  - Low: 172 (29.5) vs. 72 (36.7)
  - Moderate: 105 (18) vs. 31 (15.8)
  - Severe: 216 (37) vs. 65 (33.2)
  - None: 366 (62.5) vs. 11 (57.8)
  - Low: 67 (11.4) vs. 29 (15.1)
  - Moderate: 55 (9.4) vs. 20 (10.4)
  - Severe: 98 (16.7) vs. 32 (16.7)
  - None: 312 (52.7) vs. 86 (45)
  - Low: 111 (18.8) vs. 43 (22.5)
  - Moderate: 92 (15.5) vs. 25 (13.1)
  - Severe: 77 (13) vs. 37 (19.4)
  - None: 360 (61.6) vs. 103 (53.1)
  - Low: 42 (7.2) vs. 18 (9.3)
  - Moderate: 79 (13.5) vs. 29 (15)
  - Severe: 103 (17.6) vs. 44 (22.7)
  - MetMet + ValMet: 235 (38.2) vs. 73 (36.9)
  - ValVal: 380 (61.8) vs. 125 (63.1)

- **Physical abuse**
  - None: 180 (30.6) vs. 58 (30.2)
  - Low: 134 (22.8) vs. 34 (17.7)
  - Moderate: 72 (12.2) vs. 35 (18.2)
  - Severe: 202 (34.4) vs. 65 (33.9)
  - None: 91 (15.6) vs. 28 (14.3)
  - Low: 172 (29.5) vs. 72 (36.7)
  - Moderate: 105 (18) vs. 31 (15.8)
  - Severe: 216 (37) vs. 65 (33.2)
  - None: 366 (62.5) vs. 11 (57.8)
  - Low: 67 (11.4) vs. 29 (15.1)
  - Moderate: 55 (9.4) vs. 20 (10.4)
  - Severe: 98 (16.7) vs. 32 (16.7)
  - None: 312 (52.7) vs. 86 (45)
  - Low: 111 (18.8) vs. 43 (22.5)
  - Moderate: 92 (15.5) vs. 25 (13.1)
  - Severe: 77 (13) vs. 37 (19.4)
  - None: 360 (61.6) vs. 103 (53.1)
  - Low: 42 (7.2) vs. 18 (9.3)
  - Moderate: 79 (13.5) vs. 29 (15)
  - Severe: 103 (17.6) vs. 44 (22.7)
  - MetMet + ValMet: 235 (38.2) vs. 73 (36.9)
  - ValVal: 380 (61.8) vs. 125 (63.1)

- **Sexual abuse**
  - None: 180 (30.6) vs. 58 (30.2)
  - Low: 134 (22.8) vs. 34 (17.7)
  - Moderate: 72 (12.2) vs. 35 (18.2)
  - Severe: 202 (34.4) vs. 65 (33.9)
  - None: 91 (15.6) vs. 28 (14.3)
  - Low: 172 (29.5) vs. 72 (36.7)
  - Moderate: 105 (18) vs. 31 (15.8)
  - Severe: 216 (37) vs. 65 (33.2)
  - None: 366 (62.5) vs. 11 (57.8)
  - Low: 67 (11.4) vs. 29 (15.1)
  - Moderate: 55 (9.4) vs. 20 (10.4)
  - Severe: 98 (16.7) vs. 32 (16.7)
  - None: 312 (52.7) vs. 86 (45)
  - Low: 111 (18.8) vs. 43 (22.5)
  - Moderate: 92 (15.5) vs. 25 (13.1)
  - Severe: 77 (13) vs. 37 (19.4)
  - None: 360 (61.6) vs. 103 (53.1)
  - Low: 42 (7.2) vs. 18 (9.3)
  - Moderate: 79 (13.5) vs. 29 (15)
  - Severe: 103 (17.6) vs. 44 (22.7)
  - MetMet + ValMet: 235 (38.2) vs. 73 (36.9)
  - ValVal: 380 (61.8) vs. 125 (63.1)
| Emotional abuse | None | 35.6 (14.2) | 2.36 (3.2) | 204 (34.2) | 1/3 | 33 (18.9) | F=18; dl=3/764; p<0.001 |
| Low | 32.7 (13.7) | 2.9 (3.2) | 127 (21.3) | 39 (22.3) | X2=16.34; dl=3; p=0.001 |
| Moderate | 30.9 (11.8) | 3.3 (3.3) | 76 (12.8) | 29 (16.5) | X2=10.66; dl=3; p=0.014 |
| Severe | 27.1 (12.2) | 3.9 (5.8) | 189 (31.7) | 74 (42.3) | X2=10.66; dl=3; p=0.014 |
| Emotional neglect | None | 33 (13.3) | 2.7 (4.3) | 383 (63.9) | 1/3 | 88 (52.1) | F=16.81; dl=3/764; p<0.001 |
| Low | 33.6 (13.9) | 2.8 (3.7) | 197 (32.8) | 45 (26) | X2=14.44; dl=3; p=0.002 |
| Moderate | 29.7 (12.5) | 2.8 (3.2) | 109 (18.2) | 26 (15) | X2=12.26; dl=3; p=0.0066 |
| Severe | 29.1 (13.5) | 3.8 (5.4) | 194 (32.4) | 83 (48) | X2=11.26; dl=3; p=0.01 |
| Physical abuse | None | 33.1 (13.8) | 2.6 (3.1) | 383 (63.9) | 1/3 | 88 (52.1) | F=16.81; dl=3/764; p<0.001 |
| Low | 29.1 (11.4) | 3.3 (3.9) | 75 (12.5) | 19 (11.2) | X2=12.66; dl=3; p=0.005 |
| Moderate | 29.1 (14.2) | 3.5 (4.5) | 54 (9) | 20 (11.8) | X2=12.26; dl=3; p=0.0066 |
| Severe | 28 (13.2) | 4.6 (7.3) | 87 (14.5) | 42 (24.9) | X2=12.26; dl=3; p=0.0066 |
| Physical neglect | None | 32.2 (13.5) | 2.8 (3.4) | 322 (53.4) | 1/3 | 73 (42.4) | F=18.66; dl=3/764; p<0.001 |
| Low | 30.5 (13.6) | 3.2 (5.8) | 115 (19.1) | 36 (20.9) | X2=8.69; dl=3; p=0.004 |
| Moderate | 31.2 (14.2) | 3.1 (3.2) | 88 (14.6) | 28 (16.3) | X2=6.15; dl=3; p=0.01 |
| Severe | 28.9 (14.3) | 4.2 (5.5) | 76 (12.9) | 35 (20.4) | X2=6.15; dl=3; p=0.01 |
| Sexual abuse | None | 33.6 (13.7) | 2.6 (3.5) | 383 (63.6) | 1/3 | 76 (45.2) | F=10.95; dl=3/764; p<0.001 |
| Low | 29.7 (14) | 2.9 (3.4) | 47 (7.8) | 12 (7.1) | X2=22.18; dl=3; p=0.0044 |
| Moderate | 28 (13) | 3.7 (4.2) | 72 (12) | 35 (20.8) | X2=13.11; dl=3; p=0.0044 |
| Severe | 27.3 (12) | 4.3 (6.5) | 100 (16.6) | 45 (26.8) | X2=13.11; dl=3; p=0.0044 |
| Val66Met | Met/Met + Val/Met | 31 (13.2) | 2.9 (3) | 230 (36.9) | 1/3 | 72 (40) | F=0.14; dl=1/797; p=0.7 |
| Val/Val | 31.4 (13.7) | 3.3 (5) | 393 (63.1) | 108 (60) | X2=0.67; dl=1; p=0.45 |
Table 4
Results of the multinomial regression analysis: Childhood Trauma Questionnaire as a function of Val66Met genotype

<table>
<thead>
<tr>
<th>Range</th>
<th>None</th>
<th>Low</th>
<th>Moderate</th>
<th>Severe</th>
<th>P</th>
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<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
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<tr>
<td>Met/Met+Met/Val</td>
<td>49 (41.18)</td>
<td>97 (39.75)</td>
<td>53 (38.97)</td>
<td>96 (34.16)</td>
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<tr>
<td>Val/Val</td>
<td>70 (58.82)</td>
<td>147 (60.25)</td>
<td>83 (61.03)</td>
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**Emotional neglect**

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<th>Moderate</th>
<th>Severe</th>
<th>P</th>
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<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>Met/Met+Met/Val</td>
<td>102 (42.86)</td>
<td>63 (37.5)</td>
<td>41 (38.32)</td>
<td>93 (34.83)</td>
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<tr>
<td>Val/Val</td>
<td>136 (57.14)</td>
<td>105 (62.5)</td>
<td>66 (61.68)</td>
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**Emotional abuse**

<table>
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<tr>
<th>Range</th>
<th>None</th>
<th>Low</th>
<th>Moderate</th>
<th>Severe</th>
<th>P</th>
</tr>
</thead>
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<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>Met/Met+Met/Val</td>
<td>157 (39.45)</td>
<td>59 (38.31)</td>
<td>42 (35.9)</td>
<td>36 (31.58)</td>
<td>NS</td>
</tr>
<tr>
<td>Val/Val</td>
<td>241 (60.55)</td>
<td>95 (61.69)</td>
<td>75 (64.1)</td>
<td>78 (68.42)</td>
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**Physical neglect**

<table>
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<th>Severe</th>
<th>P</th>
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<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
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<tr>
<td>Met/Met+Met/Val</td>
<td>192 (40.25)</td>
<td>34 (35.42)</td>
<td>26 (34.67)</td>
<td>42 (32.31)</td>
<td>NS</td>
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<tr>
<td>Val/Val</td>
<td>285 (59.75)</td>
<td>62 (64.58)</td>
<td>49 (65.33)</td>
<td>88 (67.69)</td>
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**Physical abuse**

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<th>Severe</th>
<th>P</th>
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<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
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<tr>
<td>Met/Met+Met/Val</td>
<td>185 (39.96)</td>
<td>23 (38.33)</td>
<td>44 (40.74)</td>
<td>44 (29.93)</td>
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<td>Val/Val</td>
<td>278 (60.04)</td>
<td>37 (61.67)</td>
<td>64 (59.26)</td>
<td>103 (70.07)</td>
<td>1.56 (1.02 – 2.4)</td>
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<th>Low</th>
<th>Moderate</th>
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**Sexual abuse**

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<th>Moderate</th>
<th>Severe</th>
<th>P</th>
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<td>N (%)</td>
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<td>N (%)</td>
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<tr>
<td>Met/Met+Met/Val</td>
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<tr>
<td>Val/Val</td>
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</table>
Figure 1: Percentage of violent suicide attempts as a function of sexual abuse and Val66Met