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

Nader Perroud, Philippe Courtet, I. Vincze, Isabelle Jaussent, Fabrice Jollant, Franck Bellivier, Marion Leboyer, Patrick Baud, Catherine Buresi, Alain Malafosse

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

N. Perroud[1], P. Courtet[2,3,4], I. Vincze[1], I. Jaussent[4], F. Jollant[2,3,4], F. Bellivier[5], M. Leboyer[5], P. Baud[1], C. Buresi[1], A. Malafosse[1,4,6]

1. Department of Psychiatry, University Hospital of Geneva, Switzerland.
2. University of Montpellier I, F-34006, France
3. Department of Psychological Medicine and Psychiatry, Lapeyronie Hospital, University Hospital of Montpellier, F-34295, France
4. INSERM U888, University of Montpellier I, Montpellier, F-34093, France
5. Département Hospitalo-Universitaire de Psychiatrie du CHU Créteil, Groupe Hospitalier Chenevier-Mondor, AP-HP, Paris, France
6. Department of Medical Genetics and Development, School of Medicine, Geneva, Switzerland

Corresponding author:
N. Perroud, Département de Psychiatrie, Belle-Idée, 2 chemin du Petit-Bel-Air, 1224 Chêne-Bourg, Geneva, Switzerland, E-mail: nader.perroud@hcuge.ch
phone: 0041/223055311
fax: 0041/223055309

Key words: BDNF, sexual abuse, childhood trauma, gene-environment interaction, Val66Met, suicide attempts

Date of submission of revised manuscript: 27 July 2007
Number of words: Abstract: 231 Introduction: 747 Discussion: 1256
Tables: 4
Figure: 1

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.

Introduction

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 a 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'-CGTGTACAAGTCTGCGTC CT-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; dl=1; p=0.05). This interaction was highly significant when considering severe sexual abuse versus none (X2=4.74; dl=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=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

Agerbo, E., Nordentoft, M. & Mortensen, P.B. (2002). Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. *BMJ* **325**, 74.

Altar, C.A., Boylan, C.B., Fritsche, M., Jackson, C., Hyman, C. & Lindsay, R.M. (1994). The neurotrophins NT-4/5 and BDNF augment serotonin, dopamine, and GABAergic systems during behaviorally effective infusions to the substantia nigra. *Exp Neurol* **130**, 31-40.

Altar, C.A., Cai, N., Bliven, T., Juhasz, M., Conner, J.M., Acheson, A.L., Lindsay, R.M. & Wieqand, S.J. (1997). Anterograde transport of brain-derived neurotrophic factor and its role in the brain. *Nature* **389**, 856-60.

Anguelova, M., Benkelfat, C. & Turecki, G. (2003). A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. *Mol Psychiatry* **8**, 646-53.

Asberg, M.. Traskman, L. & Thoren, P. (1976). 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? *Arch Gen Psychiatry* **33**, 1193-7.

Barr, C.S., Newman, T.K., Becker, M.L., Parker, C.C., Champoux, M., Lesch, K.P., Goldman, D., Suomi, S.J. & Higley, J.D. (2003). The utility of the non-human primate; model for studying gene by environment interactions in behavioral research. *Genes Brain Behav* **2**, 336-40.

Beautrais, A.L., Joyce, P.R. & Mulder, R.T. (1996). Risk factors for serious suicide attempts among youths aged 13 through 24 years. *J Am Acad Child Adolesc Psychiatry* **35**, 1174-82.

Bellivier, F., Chaste, P. & Malafosse, A. (2004). Association between the TPH gene A218C polymorphism and suicidal behavior: a meta-analysis. *Am J Med Genet B Neuropsychiatr Genet* **124**, 87-91.

Bennett, A.J., Lesch, K.P., Heils, A., Long, J.C., Lorenz, J.G., Shoaf, S.E., Champoux, M., Suomi, S.J., Linnoila, M.V. & Higley, J.D. (2002). Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry* **7**, 118-22.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E. & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry* **151**, 1132-6.

Bernstein, D.P., Ahluvalia, T., Pogge, D. & Handelsman, L. (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry* **36**, 340-8.

Bernstein, D.P. & Fink L. (1998). *Childhood Trauma Questionnaire A retrospective self-report.* The Psychological Corporation, San Antonio.

Berton, O., McClung, C.A., Dileone, R.J., Krishnan, V., Renthal, W., Russo, S.J., Graham, D., Tsankova, N.M., Bolanos, C.A., Rios, M., Monteggia, L.M., Self, D.W. & Nestler, E.J.

(2006). Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* **311**, 864-8.

Bondy, B., Buettner, A. & Zill, P. (2006). Genetics of suicide. *Mol Psychiatry* **11**, 336-51.

Brent, D.A., Baugher, M., Bridge, J., Chen, T. & Chiappetta, L. (1999). Age- and sex-related risk factors for adolescent suicide. *J Am Acad Child Adolesc Psychiatry* **38**, 1497-505.

Brent, D.A., Oquendo, M., Birmaher, B., Greenhill, L., Kolko, D., Stanley, B., Zelazny, J., Brodsky, B., Bridge, J., Ellis, S., Salazar, J.O. & Mann, J.J. (2002). Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. *Arch Gen Psychiatry* **59**, 801-7.

Brodsky, B.S., Oquendo, M., Ellis, S.P., Haas, G.L., Malone, K.M. & Mann, J.J. (2001). The relationship of childhood abuse to impulsivity and suicidal behavior in adults with major depression. *Am J Psychiatry* **158**, 1871-7.

Brown, J., Cohen, P., Johnson, J.G. & Smailes, E.M. (1999). Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. *J Am Acad Child Adolesc Psychiatry* **38**, 1490-6.

Caspi, A. & Moffitt, TE. (2006). Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci* **7**, 583-90.

Chen, Z.Y., Patel, P.D., Sant, G., Meng, C.X., Teng, K.K., Hempstead, B.L. & Lee, F.S. (2004). Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci* **24**, 4401-11.

Courtet, P., Jollant, F., Castelnau, D., Buresi, C. & Malafosse, A. (2005). Suicidal behavior: relationship between phenotype and serotonergic genotype. *Am J Med Genet C Semin Med Genet* **133**, 25-33.

Dube, S.R., Anda, R.F., Felitti, V.J., Chapman, D.P., Williamson, D.F. & Giles, W.H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. *JAMA* **286**, 3089-96.

Dwivedi, Y., Rizavi, H.S., Conley, R.R., Roberts, R.C., Tamminga, C.A. & Pandey, G.N. (2003). Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry* **60**, 804-15.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B. & Weinberger, D.R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **112**, 257-69.

Fergusson, D.M., Horwood, L.J. & Lynskey, M.T. (1996). Childhood sexual abuse and psychiatric disorder in young adulthood: II. Psychiatric outcomes of childhood sexual abuse. *J Am Acad Child Adolesc Psychiatry* **35**, 1365-74.

Fergusson, D.M., Woodward, L.J. & Horwood, L.J. (2000). Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychol Med* **30**, 23-39.

Fink, L.A., Bernstein, D., Handelsman, L., Foote, J. & Lovejoy, M. (1995). Initial reliability and validity of the childhood trauma interview: a new multidimensional measure of childhood interpersonal trauma. *Am J Psychiatry* **152**, 1329-35.

Gaspar, P., Cases, O. & Maroteaux, L. (2003). The developmental role of serotonin: news from mouse molecular genetics. *Nat Rev Neurosc* **4**, 1002-1012.

Gladstone, G., Parker, G., Wilhelm, K., Mitchell, P. & Austin, M.P. (1999). Characteristics of depressed patients who report childhood sexual abuse. *Am J Psychiatry* **156**, 431-7.

Gladstone, G.L., Parker, G.B., Mitchell, P.B., Malhi, G.S., Wilhelm, K. & Austin, M.P. (2004). Implications of childhood trauma for depressed women: an analysis of pathways from childhood sexual abuse to deliberate self-harm and revictimization. *Am J Psychiatry* **161**, 1417-25.

Gratacos, M., Gonzalez, J.R., Mercader, J.M., de Cid, R., Urretavizcaya, M. & Estivill, X. (2007). Brain-Derived Neurotrophic Factor Val66Met and Psychiatric Disorders: Meta-Analysis of Case-Control Studies Confirm Association to Substance-Related Disorders, Eating Disorders, and Schizophrenia. *Biol Psychiatry* **61**, 911-922.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F. & Weinberger, D.R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science* **297**, 400-3.

Harrington, R., Pickles, A., Aglan, A., Harrington, V., Burroughs, H. & Kerfoot, M. (2006). Early adult outcomes of adolescents who deliberately poisoned themselves. *J Am Acad Child Adolesc Psychiatry* **45**, 337-45.

Hong, C.J., Huo, S.J., Yen, F.C., Tung, C.L., Pan, G.M. & Tsai, S.J. (2003). Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology* **48**, 186-189.

Hunter, DJ. (2005). Gene-environment interactions in human diseases. *Nat Rev Genet* **6**, 287-98.

Hwang, J.P., Tsai, S.J., Hong, C.J., Yang, C.H., Lirng, J.F. & Yang, Y.M. (2006). The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. *Neurobiol Aging* **27**, 1834-7.

Iga, J.I., Ueno, S.I., Yamauchi, K., Numata, S., Tayoshi-Shibuya, S., Kinouchi, S., Nakataki, M., Song, H., Hokoishi, K., Tanabe, H., Sano, A. & Ohmori, T. (2007). The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with psychotic feature and suicidal behavior in Japanese major depressive patients. *Am J Med Genet B Neuropsychiatr Genet* In press.

Jaffee, S.R. & Price, T.S. (2007). Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Mol Psychiatry* **12**, 432-42.

Johnson, J.G., Cohen, P., Gould, M.S., Kasen, S., Brown, J. & Brook, J.S. (2002). Childhood adversities, interpersonal difficulties, and risk for suicide attempts during late adolescence and early adulthood. *Arch Gen Psychiatry* **59**, 741-9.

Kaplan, S.J., Pelcovitz, D., Salzinger, S., Mandel, F. & Weiner, M. (1997). Adolescent physical abuse and suicide attempts. *J Am Acad Child Adolesc Psychiatry* **36**, 799-808.

Karege, F., Vaudan, G., Schwald, M., Perroud, N. & La Harpe, R. (2005). Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Brain Res Mol Brain Res* **136**, 29-37.

Kim, Y.K., Lee, H.P., Won, S.D., Park, E.Y., Lee, H.Y., Lee, B.H., Lee, S.W., Yoon, D., Han, C., Kim, D.J. & Choi, S.H. (2007). Low plasma BDNF is associated with suicidal behavior in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2007 **31**, 78-85.

Kimata, H. (2005). Differential modulation of cerebrospinal fluid neurotrophins in patients with atopic dermatitis who attempted suicide. *J Clin Psychiatry* **66**, 1193-4.

Lange, A., de Beurs, E., Dolan, C., Lachnit, T., Sjollema, S. & Hanewald, G. (1999). Long-term effects of childhood sexual abuse: objective and subjective characteristics of the abuse and psychopathology in later life. *J Nerv Ment Dis* **187**, 150-8.

Lesch, KP. (2004). Gene-environment interaction and the genetics of depression. *J Psychiatry Neurosci* **29**, 174-84.

Lin, P.Y. & Tsai, G. (2004). Association between serotonin transporter gene promoter polymorphism and suicide: results of a meta-analysis. *Biol Psychiatry* **55**, 1023-30.

Li, D. & He, L. (2007). Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. *Mol Psychiatry* **12**, 47-54.

Lyons, W.E., Mamounas, L.A., Ricaurte, G.A., Coppola, V., Reid, S.W., Bora, S.H., Wihler, C., Koliatsos, V.E. & Tessarollo, L. (1999). Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. *Proc Natl Acad Sci U S A* **96**, 15239-44.

Mamounas, L.A., Blue, M.E., Siuciak, J.A. & Altar, C.A. (1995). Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J Neurosci* **15**, 7929-39.

Mann, J.J. (2003). Neurobiology of suicidal behaviour. *Nat Rev Neurosci* **4**,819-28.

Mann, J.J., Bortinger, J., Oquendo, M.A., Currier, D., Li, S. & Brent, D.A. (2005). Family history of suicidal behavior and mood disorders in probands with mood disorders. *Am J Psychiatry* **162**, 1672-9.

Martin, G., Bergen, H.A., Richardson, A.S., Roeger, L. & Allison, S. (2004). Sexual abuse and suicidality: gender differences in a large community sample of adolescents. *Child Abuse Negl* **28**, 491-503.

McHolm, A.E., MacMillan, H.L. & Jamieson, E. (2003). The relationship between childhood physical abuse and suicidality among depressed women: results from a community sample. *Am J Psychiatry* **160**, 933-8.

Moffitt, T.E., Caspi, A. & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry* **62**,473-81.

Molnar, B.E., Berkman, L.F. & Buka, S.L. (2001). Psychopathology, childhood sexual abuse and other childhood adversities: relative links to subsequent suicidal behaviour in the US. *Psychol Med* **31**, 965-77.

Murakami, S., Imbe, H., Morikawa, Y., Kubo, C. & Senba, E. (2005). Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. *Neurosci Res* **53**, 129-39.

Nelson, E.C., Heath, A.C., Madden, P.A., Cooper, M.L., Dinwiddie, S.H., Bucholz, K.K., Glowinski, A., McLaughlin, T., Dunne, M.P., Statham, D.J. & Martin, N.G. (2002). Association between self-reported childhood sexual abuse and adverse psychosocial outcomes: results from a twin study. *Arch Gen Psychiatry* **59**, 139-45.

Neves-Pereira, M., Mundo, E., Muglia, P., King, N., Macciardi, F. & Kennedy, J.L. (2002). The Brain-Derived Neurotrophic Factor Gene Confers Susceptibility to Bipolar Disorder: Evidence from a Family-Based Association Study. *Am J Hum Genet* **71**, 651-655.

Neves-Pereira, M., Cheung, J.K., Pasdar, A., Zhang, F., Breen, G., Yates, P., Sinclair, M., Crombie, C., Walker, N. & St Clair, D.M. (2005). BDNF gene is a risk factor for schizophrenia in a Scottish population. *Mol Psychiatry* **10**, 208-212.

Nurnberger, J.I., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D. & Reich, T. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry* **51**, 849-64.

Pizarro, J.M., Lumley, L.A., Medina, W., Robison, C.L., Chang, W.E., Alagappan, A., Bah, M.J., Dawood, M.Y., Shah, J.D., Mark, B., Kendall, N., Smith, M.A., Saviolakis, G.A. & Meyerhoff, J.L. (2004). Acute social defeat reduces neurotrophin expression in brain cortical and subcortical areas in mice. *Brain Res* **1025**, 10-20.

Plomin, R. & Bergeman, C.S. (1991). The nature of nurture: Genetic influence on environmental measures. *Behav Brain Sci* **14**, 373-427.

Preisig, M., Fenton, B.T., Matthey, M.L., Berney, A. & Ferrero, F. (1999). Diagnostic Interview for Genetic Studies (DIGS): Inter-Rater and Test-Retest Reliability of the French Version. *Eur Arch Psychiatry Clin Neurosci* **249**, 174-179.

Romans, S.E., Martin, J.L., Anderson, J.C., Herbison, G.P. & Mullen, P.E. (1995). Sexual abuse in childhood and deliberate self-harm. *Am J Psychiatry* **152**,1336-42.

Roy, A. (2004). Relationship of childhood trauma to age of first suicide attempt and number of attempts in substance dependent patients. *Acta Psychiatr Scand* **109**, 121-5.

Roy, A. & Janal, M. (2005). Family history of suicide, female sex, and childhood trauma: separate or interacting risk factors for attempts at suicide? *Acta Psychiatr Scand* **112**, 367-71.

Rujescu, D., Giegling, I., Sato, T., Hartmann, A.M. & Moller, H.J. (2003). Genetic variations in tryptophan hydroxylase in suicidal behavior: analysis and meta-analysis. *Biol Psychiatry* **54**, 465-73.

Savitz, J., van der Merwe, L., Stein, D.J., Solms, M. & Ramesar, R. (2007). Genotype and Childhood Sexual Trauma Moderate Neurocognitive Performance: A Possible Role for Brain-Derived Neurotrophic Factor and Apolipoprotein E Variants. *Biol Psychiatry* In Press

Scaccianoce, S., Del Bianco, P., Caricasole, A., Nicoletti, F. & Catalani, A. (2003). Relationship between learning, stress and hippocampal brain-derived neurotrophic factor. *Neuroscience* **121**, 825-8.

Sheehan, D., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R. & Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* **59**, 22-33.

Siuciak, J.A., Boylan, C., Fritsche, M., Altar, C.A. & Lindsay, R.M. (1996). BDNF increases monoaminergic activity in rat brain following intracerebroventricular or intraparenchymal administration. *Brain Res* **710**, 11-20.

Tsankova, N.M., Berton, O., Renthal, W., Kumar, A., Neve, R.L. & Nestler, E.J. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci* **9**, 519-25.

Ullman, S.E. & Brecklin LR. (2002). Sexual assault history and suicidal behavior in a national sample of women. *Suicide Life Threat Behav* **32**, 117-30.

Supported by grant from the Swiss National Foundation (#32-102168.03 and # 32-112084 to Pr A. Malafosse), Pr P Courtet was funded by the Unité de Recherche Clinique of Montpellier University Hospital (PHRC UF 7653), Dr N. Perroud received a grant from the School of Medicine from Geneva.

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

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

le 2 Childhood maltreatments among violent and non-violent suicide attempters

		Non-violent suicide attempters (N=615)	Violent suicide attempters (N=198)						
				Simple Chi-square test	Logistic regressions and Wald tests				
		N (%)	N (%)	p	Unadjusted p value comparing abused vs. non-abused individuals	Adjusted p value comparing abused vs. non-abused individuals	Unadjusted Wald test	Adjusted Wald test	Adjusted Wald test comparing severe maltreatment vs. none
motional abuse	None	180 (30.6)	58 (30.2)	X2=5.5; dl=3; p=0.137	b=0.02; SE=0.18; z=0.11; p=0.92	b=0.04; SE=0.19; z=0.21; p=0.837	X2=2.92; dl=1; p=0.088	X2=2.63; dl=1; p=0.1	NS
	Low	134 (22.8)	34 (17.7)						
	Moderate	72 (12.2)	35 (18.2)						
	Severe	202 (34.4)	65 (33.9)						
motional neglect	None	91 (15.6)	28 (14.3)	X2=3.6; dl=3; p=0.3	b=0.1; SE=0.23; z=0.44; p=0.66	b=0.058; SE=0.25; z=0.23; p=0.82	X2=0.34; dl=1; p=0.56	X2=0.31; dl=1; p=0.58	NS
	Low	172 (29.5)	72 (36.7)						
	Moderate	105 (18)	31 (15.8)						
	Severe	216 (37)	65 (33.2)						
Physical abuse	None	366 (62.5)	11 (57.8)	X2=2.3; dl=3; p=0.52	b=0.19; SE=0.17; z=1.15; p=0.25	b=0.16; SE=0.18; z=0.87; p=0.39	X2=0.02; dl=1; p=0.89	X2=0.11; dl=1; p=0.74	NS
	Low	67 (11.4)	29 (15.1)						
	Moderate	55 (9.4)	20 (10.4)						
	Severe	98 (16.7)	32 (16.7)						
Physical neglect	None	312 (52.7)	86 (45)	X2=7.3; dl=3; p=0.06	b=0.31; SE=0.17; z=1.84; p=0.065	b=0.28; SE=0.18; z=1.6; p=0.111	X2=0.87; dl=1; p=0.35	X2=0.91; dl=1; p=0.34	NS
	Low	111 (18.8)	43 (22.5)						
	Moderate	92 (15.5)	25 (13.1)						
	Severe	77 (13)	37 (19.4)						
xual abuse	None	360 (61.6)	103 (53.1)	X2=4.8; dl=3; p=0.188	b=0.35; SE=0.17; z=2.1; p=**0.036**	b=0.45; SE=0.18; z=2.49; p=**0.013**	X2=4.39; df=1; p=**0.036**	X2=3.8; dl=1; p=**0.05**	X2=4.74; dl=1; p=**0.029**
	Low	42 (7.2)	18 (9.3)						
	Moderate	79 (13.5)	29 (15)						
	Severe	103 (17.6)	44 (22.7)						
al66Met	MetMet + ValMet	235 (38.2)	73 (36.9)	X2=0.11; dl=1; p=0.735		b=-0.004; SE=0.18; z=-0.02; p=0.98			
	ValVal	380 (61.8)	125 (63.1)						

table 3 — Age at onset and number of suicide attempts as a function of childhood maltreatment and Val66Met genotype

		Age at onset of suicide attempts			Number of suicide attempts				
		Means (SD)	Uncorrected p value	Corrected p value	Means (SD)	categories 1/3 N (%)	categories More N (%)	Uncorrected p value	Corrected p value
Emotional abuse	None	35.6 (14.2)	F=18; dl=3/764; p<0.001	F=9.46; dl=3/757; p<0.001	2.36 (3.2)	204 (34.2)	33 (18.9)	X2=16.34, dl=3; p=0.001	X2=10.66; dl=3; p=0.014
	Low	32.7 (13.7)			2.9 (3.2)	127 (21.3)	39 (22.3)		
	Moderate	30 .9 (11.8)			3.3 (3.3)	76 (12.8)	29 (16.5)		
	Severe	27.1 (12.2)			3.9 (5.8)	189 (31.7)	74 (42.3)		
Emotional neglect	None	33 (13.3)	F=6.16; dl=3/763; p<0.001	F=4.96; dl=3/756; p=0.0021	2.7 (4.3)	98 (16.4)	19 (11)	X2=14.44; dl=3; p=0.002	X2=11.26; dl=3; p=0.01
	Low	33.6 (13.9)			2.8 (3.7)	197 (32.8)	45 (26)		
	Moderate	29.7 (12.5)			2.8 (3.2)	109 (18.2)	26 (15)		
	Severe	29.1(13.5)			3.8 (5.4)	194 (32.4)	83 (48)		
Physical abuse	None	33.1 (13.8)	F=6.63; dl=3/760; p<0.001	F=6.65; dl=3/753; p<0.001	2.6 (3.1)	383 (63.9)	88 (52.1)	X2=12.66; dl=3; p=0.005	X2=12.25; dl=3; p=0.0066
	Low	29.1 (11.4)			3.3 (3.9)	75 (12.5)	19 (11.2)		
	Moderate	29.1 (14.2)			3.5 (4.5)	54 (9)	20 (11.8)		
	Severe	28 (13.2)			4.6 (7.3)	87 (14.5)	42 (24.9)		
Physical neglect	None	32.2 (13.5)	F=1.86; dl=3/768; p=0.135	F=3.17; dl=3/761; p=0.0239	2.8 (3.4)	322 (53.4)	73 (42.4)	X2=8.69; dl=3; p=0.034	X2=6.15; dl=3; p=0.105
	Low	30.5 (13.6)			3.2 (5.8)	115 (19.1)	36 (20.9)		
	Moderate	31 (12.8)			3.1 (3.2)	88 (14.6)	28 (16.3)		
	Severe	28.9 (14.3)			4.2 (5.5)	78 (12.9)	35 (20.4)		
Sexual abuse	None	33.6 (13.7)	F=10.95; dl=3/763; p<0.001	F=3.81; dl=3/756; p=0.0099	2.6 (3.5)	383 (63.6)	76 (45.2)	X2=22.18; dl=3; p<0.001	X2=13.11; dl=3; p=0.0044
	Low	29.7 (14)			2.9 (3.4)	47 (7.8)	12 (7.1)		
	Moderate	28 (13)			3.7 (4.2)	72 (12)	35 (20.8)		
	Severe	27.3 (12)			4.3 (6.5)	100 (16.6)	45 (26.8)		
Val66Met	Met/Met + Val/Met	31 (13.2)	F=0.14; dl=1/797; p=0.7	F=0.16; dl=1/791; p=0.69	2.9 (3)	230 (36.9)	72 (40)	X2=0.57; dl=1; p=0.45	X2=0.88; dl=1; p=0.348
	Val/Val	31.4 (13.7)			3.3 (5)	393 (63.1)	108 (60)		

Table 4 Results of the multinomial regression analysis: Childhood Trauma Questionnaire as a function of Val66Met genotype

	Emotional neglect					
Range	None	Low	Moderate	Severe	p	
	N (%)	N (%)	N (%)	N (%)		
Met/Met+Met/Val	49 (41.18)	97 (39.75)	53 (38.97)	96 (34.16)	NS	
Val/Val	70 (58.82)	147 (60.25)	83 (61.03)	185 (65.84)		
	Emotional abuse					
Range	None	Low	Moderate	Severe	p	
	N (%)	N (%)	N (%)	N (%)		
Met/Met+Met/Val	102 (42.86)	63 (37.5)	41 (38.32)	93 (34.83)	NS	
Val/Val	136 (57.14)	105 (62.5)	66 (61.68)	174 (65.17)		
	Physical neglect					
Range	None	Low	Moderate	Severe	p	
	N (%)	N (%)	N (%)	N (%)		
Met/Met+Met/Val	157 (39.45)	59 (38.31)	42 (35.9)	36 (31.58)	NS	
Val/Val	241 (60.55)	95 (61.69)	75 (64.1)	78 (68.42)		
	Physical abuse					
Range	None	Low	Moderate	Severe	p	
	N (%)	N (%)	N (%)	N (%)		
Met/Met+Met/Val	192 (40.25)	34 (35.42)	26 (34.67)	42 (32.31)	NS	
Val/Val	285 (59.75)	62 (64.58)	49 (65.33)	88 (67.69)		
	Sexual abuse					
Range	None	Low	Moderate	Severe	p	Adjusted OR 95% IC when comparing severe vs. none
	N (%)	N (%)	N (%)	N (%)		
Met/Met+Met/Val	185 (39.96)	23 (38.33)	44 (40.74)	44 (29.93)	**0.037**	1
Val/Val	278 (60.04)	37 (61.67)	64 (59.26)	103 (70.07)		1.56 (1.02 – 2.4)

Figure 1: Percentage of violent suicide attempts as a function of sexual abuse and Val66Met