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Predictors for Self-Directed Aggression in Italian Prisoners include Externalizing Behaviors, Childhood Trauma and the Serotonin Transporter Gene Polymorphism 5-HTTLPR

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Abstract

Suicidal behavior and self-mutilation can be regarded as the expression of self-directed aggression and both are common in prison populations.

We investigated the influence of externalizing behaviors, depressive symptoms, childhood trauma, 5-HTTLPR variants on self-directed aggression (N = 145) in a group of 702 male Italian prisoners. Participants were comprehensively evaluated, including for psychiatric disorders, impulsive traits, lifetime aggressive behavior (BGHA), hostility, violent behavior during incarceration, depressive symptomatology (HDRS), childhood trauma (CTQ).

Logistic regression analysis revealed FDR corrected independent main effects of externalizing behaviors: BGHA (p=0.001), violent behavior in jail (p=0.007), extraversion (p=0.015); HDRS (p=0.0004), Axis I disorders (p=0.015), CTQ (p=0.004) and 5-HTTLPR genotype (p=0.02). Carriers of 5-HTTLPR high (L_AL_A), intermediate (L_AL_G, S_LL_A) activity variants were more likely to have exhibited self-directed aggression relative to the low activity (L_GL_G, S_LL_G, S_S) variant: High/Low: OR = 2.3, 95% CI 1.27–4.68, p=0.007; Intermediate/Low: OR = 1.96, 95% CI 1.09–3.68, p=0.025. The CTQ main effect was driven by physical abuse. There was no interactive effect of 5-HTTLPR and CTQ. Secondary logistic regression analyses in (a) all suicide attempters (N = 88) and (b) all self-mutilators (N = 104), compared with controls revealed that in both groups, childhood trauma (p = 0.008-0.01), depression (p=0.0004-0.001) were strong predictors. BGHA, violent behavior in jail predicted self-mutilation (p=0.002) but not suicide attempts (p = 0.1).

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This study was able to distinguish differing influences on self-directed aggression between groups of closely related predictor variables within the externalizing behavioral domain. 5-HTTLPR had an independent, variant dosage effect.

Keywords

Self-directed aggression; suicide attempters; self-mutilators; externalizing behaviors; BGHA; childhood trauma; CTQ; extraversion; prisoners; serotonin transporter gene polymorphism; 5-HTTLPR genotype

INTRODUCTION

Suicidal behavior and self-mutilation can both be regarded as the expression of self-directed aggression. Self-mutilation is intentional repetitive behavior that results from the failure to resist impulses to harm oneself physically (Carli *et al.*, 2011a). High comorbidity has been observed between suicide attempts and self-mutilation (Dulit *et al.*, 1994, Klonsky *et al.*, 2013, Nelson & Grunebaum, 1971, Nock *et al.*, 2006). Persistent self-mutilation may predict repeated suicide attempts (Dell'osso *et al.*, 2013, Klonsky *et al.*, 2013).

Psychiatric disorders, including substance use disorder, are predictors for suicidal behavior; over 90% of those who committed suicide had a psychiatric diagnosis at the time of death (Bertolote & Fleischmann, 2002, Goldberger *et al.*, 2015, Mann, 2002, Mattisson *et al.*, 2015, Pedersen *et al.*, 2014). Alcohol dependence was associated with suicidal ideation and suicide attempts independent of mood disorder (Glasheen *et al.*, 2015, Sung *et al.*, 2015).

Self-mutilation, like suicide attempts, has been linked to a cluster of heritable personality features, specifically borderline personality disorder (Schaffer *et al.*, 1982, Shearer *et al.*, 1988, Simeon *et al.*, 1992), obsession (Mckerracher *et al.*, 1968, Paul *et al.*, 2002), introversion, neuroticism/anxiety-related traits and antisocial behavior (Roy, 1978, Simeon *et al.*, 1992). Suicide attempters with a history of self-mutilation have higher levels of depression, hopelessness, aggression, anxiety and impulsivity and are more likely to have been exposed to childhood trauma than suicide attempters who do not self-mutilate (Stanley *et al.*, 2001).

Many studies have reported that prisoners are at risk of attempting suicide, committing suicide and of having suicidal ideation (Fazel & Danesh, 2002, Jenkins *et al.*, 2005). For example, Jenkins *et al.* (2005) found that the lifetime prevalence of suicide attempts was 27% in British male prisoners compared with 3.6% of men in the British general population. Moreover, 46% of male prisoners had experienced suicidal thoughts in their lifetime compared with 14% of the community men. Another study has shown that 77% of US prisoners who attempted suicide had psychiatric disorders compared with 15% in the general prison population (Goss *et al.*, 2002). A few studies have shown that self-mutilation is also common in prisoners (Carli *et al.*, 2011a, Horton *et al.*, 2014).

There is abundant evidence that central serotonin (5-HT) function plays an important role in impulsive aggression, including suicidal behavior (Coccaro *et al.*, 2015). Several studies

have shown that CSF levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) are lower in violent suicide attempters, persistent suicide attempters, medically damaging suicide attempts, completed suicide and violent offenders (Asberg *et al.*, 1976, Bondy *et al.*, 2006, Mann *et al.*, 1996, Roy *et al.*, 1989, Zhou *et al.*, 2005). Moreover, in a study of self-directed aggression in personality disorder patients, those with a history of suicidal and self-mutilation behaviors had decreased central 5-HT function and the decrease was greatest in those with both behaviors (New *et al.*, 1997). The serotonin transporter (5-HTT) plays a key role in regulating neuronal 5-HT by controlling 5-HT reuptake from the synaptic cleft. Two meta-analyses have shown that 5-HTTLPR, a functional promoter polymorphism in *SLC6A4*, the gene encoding the 5-HTT, is associated with suicidal behavior in a number of populations, such as Caucasian, African American, Han Chinese and Hispanic (Clayden *et al.*, 2012, De Medeiros Alves *et al.*, 2015). This common VNTR polymorphism, (44-basepair insertion/deletion) alters transcription such that short 'S' allele is associated with an approximately 50% reduction in 5-HTT availability and concomitant increase in synaptic 5-HT and reduced neuronal 5-HT uptake (Heils *et al.*, 1996). Later studies have analyzed the triallelic 5-HTTLPR that incorporates the functional single nucleotide polymorphism rs25531, A>G located on the long 'L' allele resulting in the separation of the high activity L_A allele from a third allele, L_G which predicts low 5-HTT activity similar to the S allele (Hu *et al.*, 2006).

Recent studies have provided mixed results about whether the low activity S or high activity L 5-HTTLPR allele predicts risk for suicidal behavior. Earlier studies showed that the S allele was associated with increased risk of suicidal ideation and/or suicidal behavior in different ethnic populations (Caspi *et al.*, 2003, Gibb *et al.*, 2006, Roy *et al.*, 2007, Zalsman *et al.*, 2006). A previous meta-analysis showed a strong positive association between the S allele and suicidal behavior (Li & He, 2007). In line with this meta-analysis, several later studies have found an association between the SS genotype/S allele and increased lethality of the suicide attempt (Saiz *et al.*, 2011, Wasserman *et al.*, 2007). In addition, a large case control study revealed that three female psychiatric inpatient suicide attempters were carriers of the very rare L_GL_G genotype that is functionally similar to SS (Perroud *et al.*, 2010). However, a later case/control study in an Asian sample revealed that the L allele was the risk allele in male schizophrenic suicide attempters (Hung *et al.*, 2011). Furthermore, a study in Caucasian depressed inpatients indicated that the LL genotype increased risk for suicidal behavior (Shinozaki *et al.*, 2013). A recent meta-analysis showed that the L allele was associated with increased risk for suicidal behavior in patients with psychiatric disorders (De Medeiros Alves *et al.*, 2015). At this point there are no published studies about main effects of 5-HTTLPR risk for self-mutilatory behavior.

Environmental risk factors for suicidal behavior include childhood trauma (Mann *et al.*, 1999). For example, it was shown in a general population sample that childhood physical abuse, sexual abuse and witnessing domestic violence accounted for 16% of suicide ideation and 50% of suicide attempts in women and 21% and 33% respectively in men (Afifi *et al.*, 2008). Childhood trauma has frequently been associated with self-harm and suicidal behavior in community and clinical populations (Briere & Gil, 1998, Fliege *et al.*, 2009). Prisoners with a history of self-harm and suicide attempts are more likely to have experienced childhood trauma (Carli *et al.*, 2011a).

With regard to suicidality and potential gene-environment interaction effects, studies in a group of substance dependent inpatients showed that the low activity 5-HTTLPR variant interacted with childhood trauma to predict suicidal behavior (Enoch *et al.*, 2013, Roy *et al.*, 2007). In contrast, a study in inpatients with depression showed that the high activity 5-HTTLPR variant had a main effect on suicidal behavior as well as an interactive effect with childhood trauma (Shinozaki *et al.*, 2013).

The aim of the current study was to investigate the influence of behavioral measures, childhood trauma and 5-HTTLPR on self-directed aggression in a large group of male Italian prisoners who had been evaluated for psychiatric disorders, impulsive traits, lifetime aggressive behavior and hostility, violent behavior during incarceration and childhood trauma. Because of the high comorbidity and similarities between self-mutilation and suicidality we analyzed both behaviors together as 'self-directed aggression'. An earlier study in this same sample showed a significant interaction between 5-HTTLPR and childhood trauma on both resilience and depressive severity. Specifically, among subjects exposed to severe childhood trauma only, the high activity variant was associated with lower resilience scores and increased current depressive severity compared with the low activity variant (Carli *et al.*, 2011b). Based on the findings of earlier studies described above, we hypothesized that measures of aggressive behaviors, history of psychiatric disorders, personality traits, childhood trauma and 5-HTTLPR, together with an interactive effect between 5-HTTLPR and childhood trauma, would increase risk for self-directed aggression in this sample of Italian prisoners.

METHODS

Participants

Full details of the dataset are provided in Bevilacqua et al, 2012. The participants with analyzable 5-HTTLPR genotypes included 702 male prisoners detained in the Penitentiary District of Abruzzo-Molise in central Italy.

All participants self-identified as Caucasians and ethnicity was also recorded by the interviewer. Informed consent was obtained from all participants after a detailed explanation of the study was provided by a psychiatrist. The Ethics Review Board of the University of Molise approved the study.

Psychiatric interviews were conducted by trained psychologists and psychiatrists. The Italian version of the structured Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1998) was administered. Lifetime psychiatric disorders were determined according to DSM-IV criteria.

Three hundred and nineteen of 702 prisoners (45.4%) had a lifetime history of Axis I psychiatric disorders. These disorders included major depression (35.4%), anxiety disorders (9.4%), bipolar disorder (9.4%), and an Axis I disorder comorbid with substance abuse (44.5%).

A total of 33.5% of the 702 prisoners had a lifetime DSM-IV diagnosis of substance dependence. These diagnoses included dependence on opiates (3.4%), alcohol (9.01%), cannabis (10.7%), cocaine (31.8%), and multiple substances (44.64%). Since substance dependence is a predictor of suicide attempts and aggression the term ‘any substance dependence’ (N = 235) was included in the analyses.

Externalizing behaviors: measures of aggression, hostility, impulsivity and violence directed towards self and others

Self-directed aggression: lifetime history of suicide attempt and/or self-mutilation—A lifetime history of suicide attempt and self-mutilation was assessed during the psychiatric interview conducted by trained psychologists and psychiatrists. A suicide attempt was defined as a self-destructive act with some intent to end one's life that was not self-mutilatory in nature. Self-harm acts, which were not suicidal, that did not carry any suicidal intent (e.g., no suicidal ideation/wish to die) and which involved intentional direct damage to one's body tissue by skin-cutting, biting, burning, and hitting were considered as self-mutilation. The dependent variable in analyses was self-directed aggression that included prisoners with self-mutilation behavior, suicidal behavior or both.

Brown-Goodwin Lifetime History of Aggression interview—The BGHA (Brown *et al.*, 1979) is an 11 item interview that assesses lifetime aggressive behavior during adolescence and adulthood including temper tantrums and violence against self, property and others (including authority) in various social contexts, such as family, school and work environment. The number of times each item occurred is recorded. Table S1 provides details of the scoring.

Buss-Durkee Hostility Inventory—The BDHI (Buss & Durkee, 1957) is a 75 item questionnaire developed to assess eight aspects of hostility: assault, indirect aggression, irritability, negativism, resentment, suspicion, verbal expression of negative affect and guilt. Table S1 provides details of the scoring.

The Barratt Impulsiveness Scale—The BIS (Barratt, 1965, Patton *et al.*, 1995) is a 30-item, 4 point Likert scale questionnaire that investigates personality/behavioral impulsiveness, including cognitive impulsiveness, motor impulsiveness and lack of planning. Table S1 provides details of the scoring.

Violent behavior during incarceration—Prisoners were recorded as having exhibited violent behavior during their incarceration if there were disciplinary reports of physical aggression or assault against other inmates or prison officers while in prison. Verbal aggression and behaviors other than physical violence (for example drug dealing) were excluded from the definition of the variable.

Assessment of depressive symptoms

The Hamilton Depression Rating scale (HDRS) (Hamilton, 1960) was completed. On the HDRS the 17 items pertaining to symptoms of depression were obtained (Fleck *et al.*, 1995).

Assessment of resilience

Resilience was assessed by the Connor-Davidson Resilience Scale (CD-RISC), which is a 25-item self-reported instrument that measure the ability to cope with stress and adversity (Connor & Davidson, 2003).

Assessment of personality traits

Eysenck Personality Questionnaire—Prisoners completed the Eysenck Personality Questionnaire (EPQ) that is a 69-item version specifically adapted for the Italian language based on the original version of the EPQ (Eysenck, 1975a, Eysenck, 1975b). EPQ psychoticism, neuroticism and extraversion scores were obtained. Extraversion can be regarded as an externalizing behavior.

Childhood trauma questionnaire (CTQ)

Prisoners completed the CTQ-34 item version (Bernstein *et al.*, 1997). The CTQ is an instrument for assessing the 5 subscales of physical abuse (PA), physical neglect (PN), emotional abuse (EA), emotional neglect (EN) and sexual abuse (SA) each assessed on a 5-point Likert scale. The 34-item CTQ was converted into the 28-item version according to accepted criteria since this is the most recent and commonly used form of the questionnaire (Bernstein *et al.*, 2003). CTQ subscale scores range from 5 to 25 and the total scores from 25 to 125. Reliability and validity of the Childhood Trauma Questionnaire have been previously demonstrated (Bernstein *et al.*, 1997, Bernstein *et al.*, 1994). Continuous CTQ scores were used in all analyses.

Genotyping

DNA was extracted from whole blood using standard protocols.

Triallelic 5-HTTLPR Genotyping—Genotyping was performed in two stages using size discrimination for the S (103bp) and L (146bp) alleles and for the rs25531 (L_A (146bp) and L_G (61bp)) alleles. The 5-HTTLPR region was amplified in a 20µl reaction: 1x Optimized Buffer A, 1x PCR enhancer, 0.25µM of each primer [FAM-ATCGCTCCTGCATCCCCATTAT (forward primer), GAGGTGCAGGGGATGCTGGAA (reverse primer)], 0.125µM of dNTP, 10ng of DNA, 1.25u of Platinum Taq polymerase (all from Invitrogen Corp., Carlsbad, CA). The PCR conditions were: 95°C (5 min), 40 cycles of 94°C (30sec), 52 °C (30sec), 68°C (1 min), and a final elongation, 68°C (10 min). S and L genotypes were discriminated directly from the PCR reaction products. The rs25531 L_A and L_G genotypes was determined by digesting 5µl PCR mix with 100 units of MspI, 1x NEB restriction buffer 1, incubated at 37°C for 1 hour (New England Biolabs). Samples were mixed with deionized formamide and GeneScan™-500 ROX Size Standard (Applied Biosystems, Foster City, CA), and the genotypes were resolved on a 3730 DNA Analyzer, data analyzed using GeneMapper 4.0 software (Applied Biosystems, Foster City, CA). Genotyping accuracy was determined empirically by duplicate genotyping of 25% of the samples selected randomly. The error rate was <0.005, and the completion rate was >0.98.

Triallelic 5-HTTLPR genotyping revealed the following allele frequencies: S = 0.44, L_A = 0.52, L_G = 0.04. Alleles were grouped as low activity (SS, S L_G, L_GL_G) (0.23), intermediate activity (S L_A, L_AL_G) (0.49) and high activity (L_AL_A) (0.28) variants (Table S2). All genotypes for S/L alleles and rs25531 were in Hardy Weinberg Equilibrium ($p > 0.64$). The distribution of the high, intermediate and low activity variants in the current study is similar to the distribution in other Caucasian male samples (Hu *et al.*, 2006).

Statistical analysis

Logistic regression analyses with self-directed aggression (attempted suicide and or self-mutilation) as the dependent variable were undertaken using JMP 11 software and generated likelihood ratio (L-R) χ^2 results. A backward-stepwise multivariable-logistic regression was performed with predictor variables being eliminated from the model in an iterative process if the level of significance was $p > 0.1$.

The continuous variables (including age, BGHA, BDHI, BIS, CTQ continuous score, EPQ psychoticism, neuroticism and extraversion, HDRS, CD-RISC) and the dichotomous variables (including any substance dependence diagnosis, violent behavior in jail, Axis I psychiatric disorder) were initially included as biologically and clinically plausible predictor variables. 5-HTTLPR genotype (high, intermediate, low activity) was included as a predictor variable. Interaction terms were also considered in the model.

Because the total CTQ score had a significant independent effect on the dependent variable in the logistic regression analysis, a secondary analysis was performed in order to determine which subscale contributed the signal. The 5 subscale scores were all entered into the whole model to determine whether any of the subscales had an independent effect on the dependent variable. If so, the relevant 5-HTTLPR \times CTQ subscale interaction term was included.

To correct for multiple comparisons a False Discovery Rate (FDR) correction was performed.

RESULTS

A total of 145 (20.7%) of 702 prisoners had engaged in self-directed aggressive behaviors. Full demographics and statistical comparisons for the four groups: self-mutilators (N = 57), suicide attempters (N = 41), self-mutilators + suicide attempters (N = 47) and controls (non-self-harming prisoners, N = 557) are provided in Table 1. After FDR correction, there were no significant differences in any measures between the 3 groups of prisoners with self-directed aggression. In contrast, the controls had significantly lower measures of aggression/impulsivity (BGHA, BDHI, BIS, violent behavior in jail ($p=0.0001$ for each)), extraversion, neuroticism ($p=0.001$ for each), psychoticism ($p=0.0003$), CTQ, HDRS ($p=0.0001$ for each) compared with the three groups of self-harming prisoners, that also remain significant after FDR correction (Table 1).

Since the three groups of prisoners with self-directed aggression did not differ significantly in demographics they were combined into one group as the dependent variable in the logistic regression analysis.

Primary analyses

In the logistic regression analysis for independent effects of predictor variables on self-directed aggressive behavior (Table 2) we observed main effects of 5-HTTLPR genotype ($p=0.02$), BGHA ($p<0.0004$), violent behavior in jail ($p=0.004$), extraversion ($p=0.013$), HDRS ($p<0.0001$), Axis I disorders ($p=0.013$), and CTQ ($p = 0.002$). There were no effects of age ($p=0.6$), any substance dependence ($p=0.67$), 5-HTTLPR \times CTQ interaction term ($p = 0.35$) or any other interaction terms. The whole model accounted for 23% of the variance in self-directed aggressive behaviors. Those also remained significant after FDR correction.

As mentioned, there was a main effect of 5-HTTLPR on self-directed aggressive behaviors; prisoners who were carriers of high and intermediate activity variants were more likely to have exhibited lifetime self-directed aggressive behaviors: High/Low: odds ratio = 2.3, 95% CI = 1.27–4.68, $p=0.007$; Intermediate/Low: odds ratio = 1.96, 95% CI = 1.09–3.68, $p=0.025$).

To illustrate the effect of 5-HTTLPR variants on self-directed aggressive behaviors we performed a contingency analysis that showed variant dosage effect of 5HTTLPR on self-directed aggressive behavior (L-R $\chi^2 = 8.5$, $p=0.014$; Pearson $\chi^2 = 8.1$, $p=0.017$) (Figure 1).

Secondary analyses with the 5 CTQ subscales continuous scores

Since the total CTQ score had a significant effect ($p = 0.002$) we conducted secondary analyses to determine which subscale might be providing the signal. Only childhood physical abuse had an independent effect on self-directed aggressive behaviors ($p = 0.01$). There was no interactive effect between physical abuse and 5-HTTLPR variants on the outcome measure ($p = 0.84$).

Secondary logistic regression analyses conducted separately in (a) all suicide attempters and (b) all self-mutilators, compared with controls

In order to determine which predictors of self-directed aggression are more prominent in suicide attempters ($N = 88$) and which are more prominent in self-mutilators ($N = 104$) relative to controls, we conducted separate secondary logistic regression analyses in these two self-directed aggression groups. The results are provided in Tables S3 and S4. In both groups, childhood trauma ($p = 0.008 - 0.01$) and depression (HDRS, $p = 0.0004-0.001$) are strong predictors. Axis I disorders are more strongly associated with suicide attempts ($p = 0.02$) than with self-mutilation ($p = 0.06$). However, aggression, as measured by the BGHA and violent behavior in jail are strong predictors of self-mutilation ($p = 0.002$) but not of suicide attempts ($p = 0.1$). 5-HTTLPR did not have a main effect ($p = 0.2 - 0.06$) in either logistic regression analysis however this is likely due to the reduced sample size.

Discussion

This study sought to identify independent predictors of self-directed aggression (suicidal behavior and/or self-mutilation), in a large sample of incarcerated Italian men. Both suicidal behavior and self-mutilation are more common in prisoners than the general population and these behaviors are frequently comorbid (Carli *et al.*, 2011a, Fazel & Danesh, 2002, Horton *et al.*, 2014, Jenkins *et al.*, 2005, Stanley *et al.*, 2001). Indeed, one third of our sample with

self-directed aggression had a lifetime history of both suicidal behavior and self-mutilation. Because of these reasons, and since demographic data did not vary between the three groups (Table 1), we felt justified to include them in one 'self-directed aggression' phenotype.

The logistic regression analysis of self-directed aggression was able to distinguish differing influences between groups of closely related predictor variables. Lifetime aggressive behavior (BGHA) and violent behavior in jail strongly predicted self-directed aggression but hostility (BDHI) had no effect. Extraversion was a predictor, but not impulsivity (BIS). There were congruent influences of current depressive symptoms as measured by the HDRS and any Axis 1 disorder (35% major depression) but neuroticism and psychoticism had no independent effect.

The association of aggressive behaviors with suicide risk has been shown in clinical populations, cohort studies in epidemiological samples, and retrospective studies of completed suicides and attempters in general population and prisoner samples (Sarchiapone *et al.*, 2009a, Sarchiapone *et al.*, 2009b, Turecki, 2005). Our study also showed that suicide attempters and self-mutilators, separately and grouped together, had higher BGHA scores and exhibited more violent behavior in jail compared with controls (Tables 1 and 2). However, when several predictor variables were included in the logistic analysis of the suicide attempter group, aggressive behavior dropped out as a predictor of suicidal behavior (Table S3). It was, however, a strong predictor of self-mutilatory behavior (Table S4).

Many studies in community, clinical and prisoner samples have shown an association between childhood trauma and self-harm and suicidal behavior (Briere & Gil, 1998, Fliege *et al.*, 2009). As expected, in this study, childhood trauma proved to be a risk factor predisposing prisoners to increased risk of self-directed aggressive behaviors. The CTQ subscale that drove this association was physical abuse which was not the most common CTQ subscale (22% of the sample); physical neglect was the most common (47%). This result corresponds with an earlier finding in a sample of criminal offenders: childhood physical abuse increased the risk of both lifetime aggressive behavior and suicide attempt (Swogger *et al.*, 2011).

High level of neuroticism has been associated with increased risk for suicide (Brezo *et al.*, 2006, Roy, 2003, Tsoh *et al.*, 2005). Moreover, high levels of neuroticism and low levels of extraversion have been significantly associated with suicidality in a general population sample (Fang *et al.*, 2012). Congruent studies have shown that higher levels of extraversion predict a lower risk for suicide, whereas introversion increases suicide risk (Roy, 2003, Tsoh *et al.*, 2005). In concurrence with these earlier studies, we found that the prisoners with suicidal behavior and also the prisoners with self-mutilatory behavior had significantly higher neuroticism scores and lower extraversion scores than the controls. However, when depressive symptomatology (HDRS score) and Axis 1 disorders were included in the logistic regression model, neuroticism was no longer a predictor. Only extraversion had an independent effect on self-directed aggressive behaviors.

This study revealed a main effect of 5-HTTLPR variants: the high and intermediate activity variants predicted self-directed aggressive behavior with a variant dosage effect. However,

there was no interactive ($G \times E$) effect with childhood trauma. Several earlier studies have shown an interactive effect between the 5-HTTLPR low activity variant and childhood trauma or stressful life events, for example on suicidal ideation in a large community cohort (Caspi *et al.*, 2003), suicidal ideation in children (Cicchetti *et al.*, 2007), suicide attempts in psychiatric inpatients (Gibb *et al.*, 2006) and suicidal behavior in substance dependent inpatients (Enoch *et al.*, 2013, Roy *et al.*, 2007). However, there have also been negative 5-HTTLPR studies for $G \times E$ effects on suicidal behavior (Coventry *et al.*, 2010, Zalsman *et al.*, 2006) and a study in depressed inpatients found an interactive effect between the 5-HTTLPR high activity variant and childhood trauma on risk for suicidal behavior (Shinozaki *et al.*, 2013)..

As discussed earlier, results of numerous studies are conflicting as to whether it is the low activity 5-HTTLPR variant (Caspi *et al.*, 2003, Gibb *et al.*, 2006, Roy *et al.*, 2007, Zalsman *et al.*, 2006), or the high activity variant (de Medeiros Alves *et al.*, 2015, Hung *et al.*, 2011, Shinozaki *et al.*, 2013) that is associated with increased risk for suicidal behavior. Another recent meta-analysis has shown a significant association, between the 5-HTTLPR low activity variant and violent suicidal behavior at least in Caucasians but indicates that the high activity variant could confer risk in Asian populations (Antypa *et al.*, 2013). It should be noted that the phenotype under analysis in the current study is self-directed aggression that also includes self-mutilation. To date, there is only one reported publication on the role of 5-HTTLPR in self-mutilation. The 5-HTTLPR low activity variant interacted with chronic interpersonal stress to predict self-mutilation in two independent samples of children (Hankin *et al.*, 2015). In our study we detected a main effect, not a $G \times E$ effect, of the high activity variant. In this context it is interesting to note that the 5-HTTLPR high activity variant has been associated with negative mood and poorer affect regulation in young adults at risk for alcoholism (Lovallo *et al.*, 2014). Moreover, an earlier study in the Italian prisoner population showed that the high activity variant was associated with lower resilience scores and increased current depressive severity, particularly among subjects exposed to severe childhood trauma (Carli *et al.*, 2011b). Clearly, data on the role of 5-HTTLPR in self-directed aggression are controversial. Sex specific effects, difference in the nature and duration of early life stressors and the specific composition of the study sample may explain discrepancies in the results of studies reporting the low transcriptional activity vs high activity as a vulnerability factor for stress reactivity.

There are several strengths to this study. Firstly, we had access to a large, extreme sample of individuals who have been incarcerated for committing an offence. Secondly, we were able to analyze several aspects of this heterogeneous phenotype 'aggression' as predictors for self-directed aggression: overt aggression and violence, indirect aggression, hostility and impulsive personality traits. Thirdly, we had a rich data set of predictor variables and were therefore able to distinguish those variables that had an independent effect on self-directed aggression.

Limitations of this study include the fact that the sample sizes for the three groups of prisoners with self-directed aggression were relatively modest and therefore individual logistic regression analysis of each of the three groups was not feasible. Moreover, all the questionnaires are self-report, and the CTQ does not include an exhaustive list of the

potentially traumatic events that could be experienced in childhood. Self-directed aggression was coded from lifetime history therefore the temporal relationship between some of the predictor variables (e.g. Axis 1 psychiatric disorders) and self-directed aggression is unclear. Finally, given mixed results reported with related phenotypes, replication studies are important to clarify the relationship between 5-HTTLPR and self-directed aggression.

In conclusion, this study in male Caucasian Italian prisoners has shown that certain externalizing behaviors (lifetime aggressive behavior (BGHA), violent behavior in jail, extraversion) strongly predicted self-directed aggression. There were also consistent influences of internalizing behaviors (current depressive symptoms (HDRS), any Axis 1 disorder). Childhood trauma proved to be another independent risk factor. Although there was a main effect of 5-HTTLPR: the high and intermediate activity variants predicted self-directed aggressive behavior with a variant dosage effect, there was no interactive effect with childhood trauma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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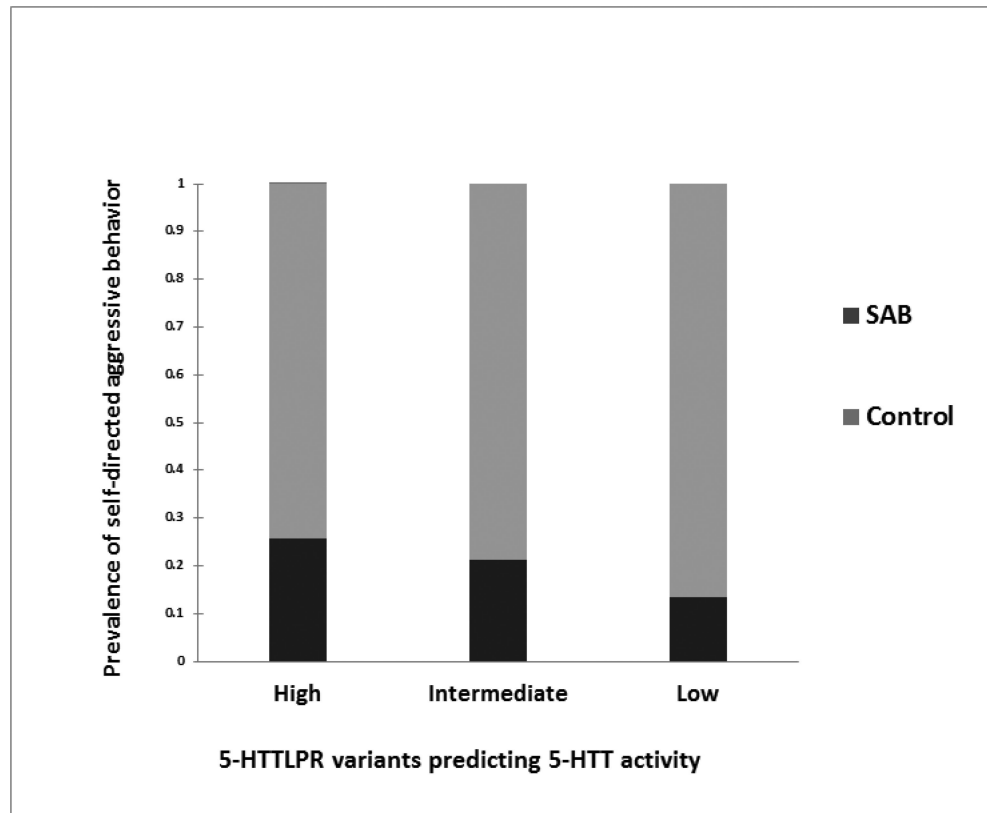


Fig 1. Independent effects of 5HTTLPR on self-directed aggressive behavior

Contingency analysis of self-directed aggressive behavior by 5-HTTLPR functional activity variants shows a variant dosage effect (L-R $\chi^2 = 8.5$, $p=0.014$; Pearson $\chi^2 = 8.1$, $p=0.017$). Triallelic 5-HTTLPR genotypes were grouped as low activity (SS, SL_G, L_GL_G), intermediate activity (SL_A, L_AL_G) and high activity (L_AL_A) variants.

Table 1

Demographic data for the four groups of Italian prisoners: controls, self-mutilators, suicide attempters and self-mutilators + suicide attempters.

	Controls N=557	Comparisons between controls and the 3 self-harm groups p	FDR p	Self-mutilation only N=57	Suicide attempters only N=41	Self-mutilation & suicide attempters N=47	Comparison across 3 self-harm groups p	FDR p
Age	40.5±11.1	0.3	0.3	37.9±9.6	41.5±9.9	40.1±10.4	0.2	0.45
BGHA	33.9±10.1	0.0001	0.0001	45.2±11.3	39.4±13.0	44.7±12.1	0.04	0.16
BDHI	35.7±10.8	0.0001	0.0001	41.6±12	37.9±12.5	40.8±11.2	0.3	0.45
BIS	46.6±14.9	0.0001	0.0001	55.3±16.6	46.9±14.1	51.8±17.1	0.04	0.16
Extraversion	14.1±3.4	0.001	0.001	13±3.9	12.1±4.3	12.2±3	0.45	0.54
Neuroticism	11.4±4.5	0.001	0.001	14.2±5.2	14.1±5.2	15.6±4.1	0.27	0.45
Psychoticism	5.2±2.9	0.0002	0.0003	6.8±3.4	6.0±3.3	6.3±3.1	0.43	0.54
HDRS	6.2±5.5	0.0001	0.0001	9.8±6.5	11.5±7.8	13.8±8.1	0.25	0.45
CD-RISC	66.9±13	0.0001	0.0001	61±12.9	60.6±13.9	58.5±16.1	0.65	0.65
Violent behavior in jail	103(18.5%)	0.0001	0.0001	30(52.6%)	11(26.8%)	22(46.8%)	0.03	0.16
Axis I	218(39.1%)	0.0001	0.0001	35(61.4%)	29(70.7%)	37(78.7%)	0.15	0.45
CTQ total continuous score	37.6±10.5	0.0001	0.0001	47.7±15.2	46.2±16.6	49.6±22.5	0.5	0.54

± Standard deviation

BGHA- Brown-Goodwin Lifetime History of Aggression

BDHI- Buss Durkee Hostility Inventory

BIS- Barratt Impulsiveness Scale

HDRS- Hamilton Depression Rating Scale

CD-RISC- Connor-Davidson Resilience Scale

Extraversion, neuroticism, and psychoticism scores derive from the Eysenck Personality Questionnaire

CTQ- Childhood Trauma Questionnaire

Axis I DSM-IV lifetime psychiatric disorders included major depression (35.4%), anxiety disorders (9.4%), bipolar disorder (9.4%), and an Axis I disorder comorbid with substance abuse (44.5%).

Table 2

Primary analysis: Independent predictors for self-directed aggressive behavior

Variable	Controls N=557	Suicide attempters/self-mutilators N=145	L-R χ^2	P	FDR p
BGHA	33.9±10.1	43.4±12.3	12.6	0.0004	0.001
Violent behavior in jail			8.1	0.004	0.007
Extraversion	14.1±3.4	12.48±3.7	6.2	0.013	0.015
5-HTTLPR			7.7	0.02	0.02
CTQ total continuous score	37.6±10.5	47.1±18.2	9.9	0.002	0.004
HDRS	6.2±5.5	11.56±7.6	17.7	<0.0001	0.0004
Axis I disorders			6.2	0.013	0.015
Whole model			162.8	<0.0001	0.0004
Whole model variance, df			0.23, 8		

± Standard deviation

L-R χ^2 = Likelihood Ratio chi square; df = degrees of freedom

5-HTTLPR H v I v L: high activity variant vs intermediate activity variant vs low activity variant

Extraversion scores derive from the Eysenck Personality Questionnaire

BGHA- Brown-Goodwin History of Aggression

HDRS- Hamilton Depression Rating Scale

CTQ- Childhood Trauma Questionnaire

Axis I psychiatric disorders- DSM IV criteria

The variance inflation factor (VIF) for each of the independent variables ranged from 1.1 to 1.5, indicating that the model is stable.