



Brief report

Interaction of 5-HTTLPR genotype and unipolar major depression in the emergence of aggressive/hostile traits

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ABSTRACT

Objective: The 5-HTTLPR polymorphism has been associated both with depression and aggression/hostility. The multidirectional association between depression, aggression and the s allele may be important, since all these phenomena are related to suicidal behavior. Our aim was to investigate the association between 5-HTTLPR and aggressive/hostile traits in depressed patients and controls.

Methods: 137 depressive and 118 control women completed the Buss–Durkee Hostility Inventory and were genotyped for 5-HTTLPR. BDHI scores in the different groups were investigated by Generalized Linear Model Analysis. Association between dependent and independent variables in the model was tested by the likelihood ratio Chi-square statistic.

Results: Diagnosis and genotype showed a significant association with several aggressive/hostile traits. Interaction of the two main effects was also significant in case of several subscales. Post hoc analyses indicated a significant association between BDHI subscales and s allele only in the depressed group.

Limitation: Only women were studied and since gender differences are present both in aggressive behavior and putatively in the behavioral effects of 5-HTTLPR genotype, our findings pertain only to females.

Conclusion: Our results indicate a robust relationship between aggression/hostility and 5-HTTLPR genotype, but this association is more marked in the presence of depression. The presence of the s allele thus not only contributes to a higher risk of depression, but in depressives also leads to higher aggression/hostility. Our results have important implications for suicide research, since the s allele is associated with violent suicide, and this association may be mediated through the emergence of increased aggression/hostility in depressed patients carrying the s allele.

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1. Introduction

Aggression and hostility are among the most widely studied aspects of human behavior (Vassar and Hale, 2009; Hennig et al., 2005), representing two faces of the same phenomena, with aggression carrying the motor component and hostility the emotional and cognitive aspect of intentionally delivering

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noxious stimuli to another organism (Buss, 1961; Buss and Durkee, 1957). Depression and aggression have been associated since the early psychodynamic theories of Abraham and Freud postulated that anger turned inward is at the core of depression (Freud, 1917; Bibring, 1953; Biaggio and Godwin, 1987). The relationship between aggression and depression is supported by epidemiological studies reporting that depressive illness is extremely common in cultures which strongly prohibit physical aggression of any form (Kendell, 1970), however, empirical research concerning the association between aggression and depression yielded conflicting results, and there is still no agreement concerning the presence, direction and etiology of aggression/hostility in depression (Weissman et al., 1971; Riley et al., 1989; Gershon et al., 1968; Wessman et al., 1960; Blackburn, 1974; Fava et al., 1982). However, the studies between aggression/hostility and depression are mainly correlational and offer little information about the possible causative relationship between these phenomena (Riley et al., 1989). Aggression and depression may be the manifestations of a common predisposing factor, which can be genetic, constitutional or experiential in nature, leading independently to depression and altered expression of hostility, but deficits in expression of hostility may also increase susceptibility for depression (Friedman, 1970).

The 5-HTTLPR polymorphism of the serotonin transporter gene was reported to be associated with aggression in animals (Heinz et al., 1998; Schwandt et al., 2010) and humans (Gonda et al., 2009; Kim et al., 2009; Beitchman et al., 2006; Gerra et al., 2005). 5-HTTLPR is also associated with affective illness (Kiyohara and Yoshimasu, 2010; Clarke et al., 2010; Lotrich and Pollock, 2004). Furthermore, the s allele of 5-HTTLPR has been linked to violent suicidal behavior (Lin and Tsai, 2004; Courtet et al., 2003; Gonda et al., in press), and this association was found to be independent from the association of suicidality and affective disorder (Bellivier et al., 2000; Roy et al., 1997; Mann, 1998) suggesting an independent effect of 5-HTTLPR on depression and suicide. It is hypothesized that the s allele predisposes to a general vulnerability which may be manifested in the emergence of any single or more distinct traits (Beitchman et al., 2006). Depression and aggression are possibly similarly independently influenced by the presence of the 5-HTTLPR s allele, which may contribute to the emergence of a common underlying factor which plays a role in both phenomena. If we postulate the role of the same predisposing factor in the background of both phenomena, we could also expect a more marked association between the 5-HTTLPR and aggressive traits and in depressed patients, where both manifestations are present.

The aim of our study was to investigate the association of the s allele of the 5-HTTLPR polymorphism with aggressive/hostile traits in major depressive and healthy control women.

2. Methods

2.1. Study subjects

137 unipolar depressive and 118 healthy women participated in our study. Patients had moderate to severe DSM-IV depression as diagnosed by their clinician and were within the first week of their psychiatric admission. Participants completed the Buss–Durkee Hostility Inventory (BDHI) and

were genotyped for 5-HTTLPR (Heils et al., 1996). DNA samples were obtained by buccal swabs.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the Scientific and Research Ethics Committee of Scientific Health Council. All subjects were given thorough explanation of the procedures of the study and all participants gave informed consent before participating in the study.

2.2. Measures

2.2.1. Buss–Durkee Hostility Inventory (BDHI)

We measured aggression and hostility using the Buss–Durkee Hostility Inventory (BDHI) (Buss and Durkee, 1957; Münnich, 1998), a 75-item true or false scored self-report inventory, including seven subscales measuring aggression and hostility, and a guilt scale.

Factor analysis by the original authors and subsequent studies confirmed the two factor concept of hostility and aggression, and the two major factors emerging were termed motor component or expressive hostility and emotional or attitudinal component or neurotic hostility, distinguishing between the experience and the expression of anger (Becker, 2007; Bushman et al., 1991; Buss and Durkee, 1957; Felsten and Leitten, 1993; Siegman et al., 1987). In our present study, we investigated the scores of the original seven subscales, the global aggression score and the aggression and hostility weighted indexes by Edmunds and Kendrick (Münnich, 1998; Edmunds and Kendrick, 1980).

2.2.2. Zung Self-Rating Depression Scale

Our psychiatrically healthy control subjects also completed the Zung Self-rating Depression scale. Since Zung established 40 points on the ZSDS as the morbidity cutoff score (Zung, 1973), we included only subjects with ZSDS scores less than 40 in our control group.

2.3. Statistical methods

Subjects were grouped according to the presence or absence of the s allele. BDHI scores in the two diagnostic groups and in the two genotype groups were investigated by Generalized Linear Model Analysis (GENMOD). Association between dependent and independent variables was tested by the likelihood ratio Chi-square statistic. Age was included as a covariate in all analyses. To investigate the effect of genotype on BDHI scores in the different study groups, post-hoc analyses were conducted comparing the different genotypes within the study groups (two post-hoc tests were run for each scale, therefore the alpha level was set to $0.05/2 = 0.025$ for these analyses). The statistical analysis was conducted using the Statistical Analysis System (SAS for Windows, version 9.1).

3. Results

We found no significant deviation in our sample from the Hardy–Weinberg equilibrium ($\chi^2 = 0.13$, $df = 1$, $p = 0.7184$). The frequency of the s allele was 39.41% in the whole sample, 41.97% in the depressed group and 36.44% in the control group. There was no significant difference in the distribution

of the s allele ($\chi^2=1.624$, $p=0.2026$, $df=1$) in the two groups. There was also no significant difference between the two groups in the distribution of genotypes ($\chi^2=1.775$, $p=0.4117$, $df=2$) and in the number of subjects carrying and not carrying the s allele ($\chi^2=1.714$, $p=0.1905$, $df=1$).

The mean age was 40.60 years (SD: 14.65) in the whole sample, 47.87 years (SD: 12.85) in the depressed group and 32.30 years (SD: 11.93) in the healthy group. There was a significant difference between mean age in the two groups ($t=10.89$, $p<0.0001$). Age showed no significant effect on BDHI scores (Table 1).

The mean values and standard deviations of the BDHI subscales in the study groups, and the χ^2 and p-values of the GENMOD analyses are summarized in Table 1. We found a significant main effect for diagnostic group in case of guilt ($\chi^2=14.7$, $p=0.000$), suspicion ($\chi^2=44.6$, $p=0.000$), indirect hostility ($\chi^2=3.8$, $p=0.053$), resentment ($\chi^2=38.9$, $p=0.000$), assault subscales ($\chi^2=5.1$, $p=0.024$), the global aggression score ($\chi^2=14.0$, $p=0.000$), and the hostility index ($\chi^2=42.0$, $p=0.000$), in all cases depressed patients scoring significantly higher (Table 1, Fig. 1A). We found a significant main effect for genotype in case of guilt ($\chi^2=8.0$, $p=0.005$), irritability ($\chi^2=4.7$, $p=0.030$), indirect hostility ($\chi^2=4.7$, $p=0.030$), negativism ($\chi^2=8.0$, $p=0.005$), resentment ($\chi^2=5.6$, $p=0.018$), and verbal aggression ($\chi^2=6.3$, $p=0.012$) subscales, and global aggression score ($\chi^2=7.3$, $p=0.007$), in all cases subjects carrying the s allele showing a higher score (Table 1, Fig. 1B). Both main effects were significant in case of guilt, indirect hostility, resentment subscales, and global aggression score. The

two-way interaction of the two main factors, diagnostic group and genotype was significant in case of guilt ($\chi^2=4.8$, $p=0.029$), irritability ($\chi^2=4.2$, $p=0.041$), resentment ($\chi^2=6.7$, $p=0.009$) subscales, the aggression index ($\chi^2=3.9$, $p=0.050$) and the global aggression score ($\chi^2=3.9$, $p=0.049$). Post hoc analyses showed that in all of these cases the two genotypes differed significantly in the depressed group (no s allele carriers < s allele carriers), but not in the control group. Although the interaction effect was not significant ($p<0.1$), post hoc analyses indicated a significantly higher score for s allele carriers in the depressed group, but not in the control group, compared to s allele non-carriers also in case of the hostility index ($\chi^2=6.6$, $p=0.010$) (Fig. 1C, Table 1).

4. Discussion

We found significant differences in the score of subscales measuring different aspects of aggression/hostility, according to psychiatric diagnosis of unipolar major depression and 5-HTTLPR genotype, as well as the interaction of these two main effects, indicating an important and complex association between aggression/hostility, depression and the s allele of the 5-HTTLPR.

In the whole sample, subjects carrying the s allele scored significantly higher in the guilt, irritability, indirect hostility, negativism, resentment, and verbal aggression subscales of the BDHI, and had a significantly higher global aggression score, which points to a robust association between the s allele of the 5-HTTLPR and aggression/hostility.

Table 1

Association of aggressive/hostile traits as measured by the Buss–Durkee Hostility Inventory with the s allele of the 5-HTTLPR and diagnostic group.

	Mean (SD)				χ^2 , p				s allele vs no s allele ^a	
	Healthy, no s allele	Healthy, s allele	Depressed, no s allele	Depressed, s allele	Diagnosis	s allele	Diagnosis × s allele	Age	Control	Depressed
<i>BDHI subscales</i>										
Guilt	3.2 (1.5)	3.4 (1.5)	3.7 (3.2)	5.1 (2.7)	$\chi^2=14.7$ p=0.000^b	$\chi^2=8.0$ p=0.005^b	$\chi^2=4.8$ p=0.029^b	$\chi^2=1.0$ p=0.315	$\chi^2=0.6$ p=0.443	$\chi^2=5.1$ p=0.024^c
Suspicion	1.6 (1.8)	1.6 (1.5)	3.5 (2.5)	3.9 (2.4)	$\chi^2=44.6$ p=0.000^b	$\chi^2=0.7$ p=0.387	$\chi^2=0.2$ p=0.655	$\chi^2=0.1$ p=0.806	$\chi^2=0.2$ p=0.672	$\chi^2=0.9$ p=0.339
Irritability	4.9 (1.4)	5.0 (1.6)	4.7 (2.2)	5.5 (2.0)	$\chi^2=0.6$ p=0.437	$\chi^2=4.7$ p=0.030^b	$\chi^2=4.2$ p=0.041^b	$\chi^2=0.7$ p=0.399	$\chi^2=0.1$ p=0.911	$\chi^2=6.5$ p=0.011^c
Indirect Hostility	3.5 (2.0)	3.8 (1.6)	3.7 (2.0)	4.5 (2.0)	$\chi^2=3.8$ p=0.053	$\chi^2=4.7$ p=0.030^b	$\chi^2=1.0$ p=0.306	$\chi^2=1.3$ p=0.250	$\chi^2=0.6$ p=0.447	$\chi^2=4.3$ p=0.038
Negativism	1.8 (1.2)	2.2 (1.4)	1.7 (1.9)	2.3 (1.6)	$\chi^2=0.5$ p=0.485	$\chi^2=8.0$ p=0.005^b	$\chi^2=1.0$ p=0.309	$\chi^2=0.0$ p=0.848	$\chi^2=2.6$ p=0.105	$\chi^2=4.6$ p=0.032
Resentment	1.3 (1.5)	1.3 (2.0)	2.4 (1.9)	3.6 (1.9)	$\chi^2=38.9$ p=0.000^b	$\chi^2=5.6$ p=0.018^b	$\chi^2=6.7$ p=0.009^b	$\chi^2=0.0$ p=0.993	$\chi^2=0.03$ p=0.863	$\chi^2=11.7$ p<0.001^c
Assault	1.7 (1.7)	1.4 (1.7)	2.1 (2.1)	2.4 (2.0)	$\chi^2=5.1$ p=0.024^b	$\chi^2=0.2$ p=0.685	$\chi^2=3.4$ p=0.067	$\chi^2=0.4$ p=0.505	$\chi^2=1.9$ p=0.169	$\chi^2=1.1$ p=0.293
Verbal Aggression	6.7 (2.7)	7.2 (2.5)	6.1 (3.0)	7.3 (3.1)	$\chi^2=0.2$ p=0.659	$\chi^2=6.3$ p=0.012^b	$\chi^2=0.7$ p=0.400	$\chi^2=0.0$ p=0.884	$\chi^2=1.7$ p=0.189	$\chi^2=4.6$ p=0.032
Global Aggression	24.7 (8.1)	25.8 (7.3)	28.0 (14.3)	34.6 (12.6)	$\chi^2=14.0$ p=0.000^b	$\chi^2=7.3$ p=0.007^b	$\chi^2=3.9$ p=0.049^b	$\chi^2=0.1$ p=0.801	$\chi^2=0.03$ p=0.595	$\chi^2=11.4$ p<0.001^c
<i>Indexes</i>										
Aggression	4.5 (1.2)	4.5 (1.1)	4.4 (1.6)	5.0 (1.5)	$\chi^2=1.0$ p=0.317	$\chi^2=3.2$ p=0.076	$\chi^2=3.9$ p=0.050	$\chi^2=0.1$ p=0.811	$\chi^2=0.02$ p=0.899	$\chi^2=7.2$ p=0.007^c
Hostility	3.0 (1.4)	3.0 (1.3)	4.4 (2.1)	5.2 (2.0)	$\chi^2=42.0$ p=0.000^b	$\chi^2=3.6$ p=0.059	$\chi^2=2.8$ p=0.093	$\chi^2=0.0$ p=0.890	$\chi^2=0.02$ p=0.879	$\chi^2=6.6$ p=0.010^c

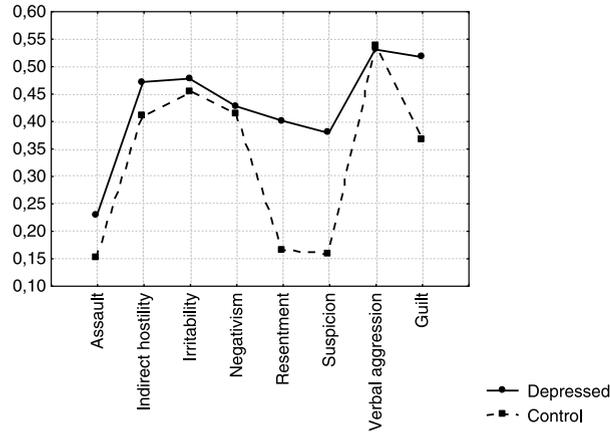
Significant results are shown in bold.

^a While 2 post-hoc tests were run for each scale, the alpha level was set to $0.05/2=0.025$.

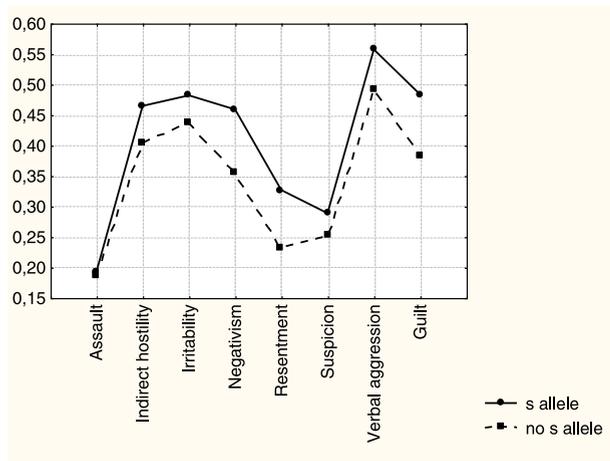
^b $p<0.05$.

^c $p<0.025$.

A) depressed patients and healthy controls (total scores on each subscale divided by the number of items in the given subscale)



B) subjects carrying and not carrying the s allele case (total scores on each subscale divided by the number of items in the given subscale)



C) depressed and control subjects carrying and not carrying the s allele (total scores on each subscale divided by the number of items in the given subscale)

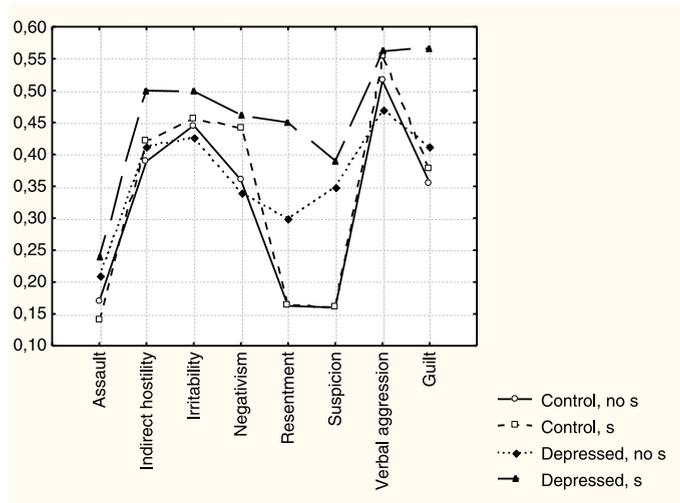


Fig. 1. Aggression/hostility trait profile.

More importantly, we also found a diagnosis \times s allele interaction in case of several subscales (guilt, resentment, and irritability subscales, aggression index, and global aggression score). However, post hoc analyses indicated that the association between the s allele of the 5-HTTLPR and these aggressive/hostile traits is present only in case of the depressed group. Depressed patients carrying the s allele score significantly higher compared to depressed subjects not carrying the s allele in all cases where the interaction effect (and also in those cases where the genotype effect only) was significant, while there is no significant difference between carriers and non-carriers of the s allele in the control group in aggressive/hostility trait scores. This finding partly contradicts earlier results, where an association between aggression and the s allele was described in nonclinical populations (Munafo et al., 2003), and the results of our previous study where we found a significant association between the s allele and several BDHI subscales in a psychiatrically healthy population (Gonda et al., 2009). However, in case of the previous studies on nonclinical samples, the authors did not control for the level of depressive symptomatology and subclinical depression, and in case of our previous and present study there is a major difference between the two populations. In the present study, all subjects in the control group had Zung Self-rating Depression Scale (ZSDS) scores below 40 and the mean score was 33.2112 (SD: 4.2403), while in the previous study they had ZSDS scores below 48 and the mean score was 36.3018 (SD: 7.0261) (Gonda et al., 2009). This difference between the results in case of the two healthy samples provides further support that the manifestation of the effect of the association between the s allele and aggressive/hostile traits may be related to depression.

Our results present important new information concerning the association between depression, aggression and the 5-HTTLPR. These results indicate a robust relationship between aggression and the presence of the s allele, but the manifestation of this association is a function of the presence of depression. This means that the presence of the s allele not only contributes to a higher risk of the emergence of depression as reported in earlier studies (Clarke et al., 2010; Lotrich and Pollock, 2004), but in depressed people it also leads to an increased chance of the manifestation of higher levels of aggression/hostility. It is well known that the s allele of the 5-HTTLPR is associated not only with depression (Clarke et al., 2010; Lotrich and Pollock, 2004) and aggression/hostility (Gonda et al., 2009), but also with violent suicidal behavior (Gonda et al., in press), and the majority of suicides are committed by patients suffering from major depression (Rihmer, 2007). It has also been reported that the association between violent suicidality and the s allele is independent from the association between affective disorders and the s allele (Bellivier et al., 2000; Mann, 1998; Roy et al., 1997). Viewed from this aspect, our results indicate that the presence of the s allele may convey increased suicide risk via two different pathways: by increasing the risk of the development of major depression, and by increasing the manifestation of aggressive/hostile traits, which is more marked in case of depressed people also according to our results and also to reports of increased anger attacks in case of unipolar but also bipolar depressives during depressive episodes (Mammen et al., 2004; Perlis et al., 2004; Fava,

1998). It is also possible that the relationship between depression and suicide is, at least in part, mediated by the 5-HTTLPR through the enhanced manifestation of aggression/hostility in depressed patients.

Our study has some limitations. Our sample is relatively small, and is all-female. Previous reports indicate significant gender differences in serotonergic function, (Nishizawa et al., 1997; Costes et al., 2005; Williams et al., 2003), in the manifestation of aggression/hostility (Bushman et al., 1991; Buss and Durkee, 1957), and depression as well (Wilhelm et al., 2008). 5-HTTLPR is also hypothesized to have opposite behavioral consequences in women and men (Brummett et al., 2008). Also, our control sample was significantly younger than the depressed group, and although age did not have a significant effect in any analyses, we cannot rule out the possibility that some of our controls will develop depression later.

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Conflict of interest

None of the authors has any conflict of interest to declare.

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