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Serotonin transporter polymorphism, depressive symptoms, and emotional impulsivity among advanced breast cancer patients

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Abstract

Purpose—This study tested a theory linking a marker of low serotonergic function to both depression and impulsivity in a sample of advanced breast cancer patients, among whom elevated depressive symptoms and difficulty regulating emotions are commonly reported.

Methods—A total of 95 patients provided blood samples for serotonin transporter polymorphic region of the gene (5-HTTLPR) and completed questionnaires that measured depressive symptoms and emotional impulsivity.

Results—Structural equation modeling revealed that the s allele of 5-HTTLPR was related to greater depressive symptoms ($\beta = .20, p < .042$) but only marginally to greater emotional impulsivity ($\beta = .19, p < .068$). Depressive symptoms and emotional impulsivity were positively related ($\beta = .33, p < .003$). Further tests explored possible mediation from genotype to one psychological variable via the other. Results suggest that depressive symptoms, particularly perceived interpersonal rejection, may be a pathway linking genotype to emotional impulsivity.

Conclusions—Findings provide the first evidence that low serotonergic function contributes to both depression and impulsivity within a clinically meaningful sample. Furthermore, the link of s allele of 5-HTTLPR to emotional impulsivity was mediated by depressive symptoms, particularly perceptions of social rejection. Findings have implications for advanced breast cancer patients' treatment decision.

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Compliance with ethical standards The study was carried out in accordance with the latest version of the Declaration of Helsinki and the study design was reviewed by the Stanford University Institutional Review Board. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Conflict of interest The authors declare that they have no conflict of interest.

Keywords

Serotonin transporter polymorphism (5-HTTLPR); Depressive symptoms; Emotional impulsivity; Advanced breast cancer; Treatment decision

Introduction

A polymorphism in the serotonin transporter gene (5-HTTLPR) has been linked to differential susceptibility to several phenomena, both emotional [1–4] and behavioral [5, 6]. Specifically, the short (*s*) allele of 5-HTTLPR, which is a marker of low serotonergic function, has been related to stress-related depressive symptoms, such as dejected mood, inertia, and social withdrawal, and also to greater impulsive tendencies, such as sensation seeking and impulsive aggression (for review see [7]).

The diversity among the correlates of low serotonergic function has led to the hypothesis that rather than being a marker of a particular problem, the *s* allele is a marker of *responsiveness to signals of emotion*, within a dimension of constraint vs impulsive reactivity [8–10]. In other words, a strong emotion of the moment (e.g., feeling dejected or irritated) is more likely to be manifested in a behavior reflecting that emotion (thus, depressed or aggressive behavior) if serotonergic function is low.

There is evidence supporting this hypothesis [11–13]. Thus far, however, the samples have been limited to normal young adults. It would seem to be important to determine whether the effect would also occur in more clinically relevant samples. Moreover, stress is known to potentiate effects of the 5-HTTLPR genotype [14, 15]. Given that, it would seem particularly useful to test these effects in highly stressed samples. This study did so using a sample of patients with advanced breast cancer.

The diagnosis and treatment of advanced stage cancer are major stressful life events [16, 17]. Elevated levels of depressive symptoms [18, 19] and difficulty in regulating emotions [20, 21] are both common among patients with advanced cancer. Yet, there is also a good deal of variation, both in depressive symptoms and in emotion-related impulsivity [22, 23].

We predicted that the *s* allele of 5-HTTLPR would relate both to elevated depression symptoms and to elevated emotional impulsivity among women with advanced breast cancer. We also predicted that depressive symptoms would positively relate to emotional impulsivity. Finally, we attempted to clarify the relations among these three variables by exploring potential mediation, such that the predictive effect of 5-HTTLPR on one would occur via differences in the other.

Methods

Participants and procedure

Participants were women diagnosed with advanced (recurrent or metastatic) breast cancer (ABC) who enrolled in a study concerned primarily with sleep functioning. Women were excluded if they had (a) previous bilateral lymph node removal; (b) had active cancers (other

than breast cancer) within the past 10 years; (c) had taken corticosteroids, glucocorticoids, or benzodiazepines within the week preceding or during their scheduled in-laboratory sleep study; (d) had a history of major psychiatric illness that required hospitalization in the preceding year; (e) had substance abuse or dependence; (f) had engaged in regular travel involving two or more time zones or shift work (e.g., working 4:00 p.m.–midnight or 10:00 p.m.–6:00 a.m.) during the 3 months before the beginning of the study; (g) had Karnofsky Performance Status Scale ratings of less than 70%; or (h) had chemotherapy or hormonal treatment within 2 months prior to participating in the study [24]. Of 545 who were contacted, 177 met these eligibility criteria. Of those, 105 enrolled and 95 had complete data for the study variables. Compared with ABC patients who provided complete data, those who did not provide complete data did not differ in study variables ($ps > .31$).

The study was carried out in accordance with the latest version of the Declaration of Helsinki and the study design was reviewed by the Stanford University Institutional Review Board. Participants were recruited by letter of request through breast cancer clinics at Stanford University, from breast surgeons and oncologists at Stanford and the University of California San Francisco (UCSF), through Army of Women mailing list, and through advertisements in local newspapers and the Internet. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Measures

Genotyping—Genotyping was performed on venous blood, at the Stanford University School of Medicine. Oligonucleotide primers flanking the 5-HTT-linked polymorphic region [25] and corresponding to the nucleotide positions –1416 to –1397 (str5, 5'-GGC GTT GCC GCT CTG AAT GC) and –910 to –888 (str3, 5'-GAG GGA CTG AGC TGG ACA ACC AC) of the 5-HTT gene 5'-flanking regulatory region were used to generate 484-bp or 528-bp fragments. The polymerase chain reaction products were electrophoresed through 5% polyacrylamide gel (acrylamide/bis-acrylamide ratio 19:1) at 60 V for 60 min. A 100-bp marker was used to measure the PCR product size for *l* and *s* alleles. Two independent observers, blind to any information pertaining to the participants, assigned the alleles and genotypes. The *ll*/homozygotes (two copies of *l* allele) were found in 29.5% of the participants, the *sl*/heterozygotes (one copy of the *s* allele) in 50.5%, and the *ss*/homozygotes (two copies of *s* allele) in 20% of our sample. This distribution was in Hardy-Weinberg equilibrium ($\chi^2 = .04, p > .10$). Analyses treated participants with the three genotypes as distinct groups, varying in the presence of the number of copies of the *s* allele from 0 (*ll*, $n = 28$), 1 (*sl*, $n = 48$), to 2 (*ss*, $n = 19$).

Depression—Depressive symptoms were measured using the 20-item Center for Epidemiologic Studies Depression scale (CES-D: [26]). Responses used a 4-point response format (0 = *rarely or none of the time* to 3 = *most or all of the time*). Higher sum scores, after reverse-coding when appropriate, represent higher depressive symptoms. This scale had good internal consistency in the present study ($\alpha = .87, M = 8.88, SD = 7.38$). About 16% of the sample had CES-D ≥ 16 , which is a common cutoff suggesting clinical level of depressive symptoms [26].

Impulsivity—Reports of impulsive reactivity to emotion were assessed using the 6-item Impulse Control Difficulties subscale of the Difficulties in Emotion Regulation Scale (DERS: [27]). Example items are “When I’m upset, I lose control over my behaviors” and “I experience my emotions as overwhelming and out of control.” Responses used a 5-point response format (1 = *almost never*; 2 = *sometimes*; 3 = *about half the time*; 4 = *most of the time*; and 5 = *almost always*). Items were summed, after reverse-coding when appropriate. Higher scores indicate greater difficulties with impulse control. This subscale had good internal consistency in the present study ($\alpha = .85$, $M = 8.66$, $SD = 3.35$).

Covariates—Self-reported age ($M = 57.67$, $SD = 7.44$) and marital status (married or in a marriage-like relationship) served as covariates in the analyses. For this purpose, marital status was condensed to two categories: currently married ($n = 55$) vs not married ($n = 40$).

Statistical analyses

The primary study aims were tested using structural equation modeling (SEM) with manifest variables [28]. Genotype, including three groups (*s/s*, *s/l*, and *l/l*), was an exogenous variable. In Model 1A, in which genotype predicted both impulsivity and depression simultaneously, impulsivity and depression were endogenous variables. In Model 1B, depression was treated as a mediator and impulsivity as an endogenous variable. In Model 1C, impulsivity was treated as a mediator and depression as an endogenous variable. Age and married vs not-married were covariates in all three models. Measurement errors between impulsivity and depression in Model 1A and between depression and being married in Model 1C were allowed to correlate with each other, which improved model fit significantly.

Three model-fit indices are reported: model chi-square, the confirmatory fit index (CFI), and the root mean squared error of approximation (RMSEA). For the model chi-square, values less than two times the degrees of freedom [29], for the CFI, values of $> .95$, and for the RMSEA measure, values of $< .06$ [30], reflect adequate fits of a specified model to the data. Significance level in all analyses was set at $p < .05$.

Results

Sample characteristics

As shown in Table 1, participants were primarily middle-aged, married, non-Hispanic White, and relatively highly educated. Overall scores of emotional impulsivity and depressive symptoms are comparable to healthy adults of similar age [27, 31]. Approximately 1 of 6 (15.8%) participants reported clinically meaningful levels of depressive symptoms (16 or above on the CES-D).

Zero-order correlations among study variables are in Table 2. Older participants were slightly more likely to have the *l/l* genotype, married participants were more likely to report lower levels of depressive symptoms, and emotional impulsivity and depressive symptoms were positively correlated.

Associations of 5-HTTLPR with impulsivity and depressive symptoms

We first tested the extent to which 5-HTTLPR predicted impulsivity and depressive symptoms simultaneously (Fig. 1a). The fit of model 1 was good: $\chi^2_{(3)} = 3.40$, CFI = .977; and RMSEA = .037. Greater presence of the s allele of 5-HTTLPR was significantly associated with greater levels of depressive symptoms ($\beta = .20$, $p < .042$) but only marginally associated with greater levels of emotional impulsivity ($\beta = .19$, $p < .068$; Fig. 1a). Emotional impulsivity and depressive symptoms were significantly positively correlated with each other ($r = .33$, $p < .003$).

The next question, more exploratory in nature, was whether either emotional impulsivity or depressive symptoms might mediate the link between 5-HTTLPR and the other measure. Model 1B (Fig. 1b) tested depressive symptoms as a mediator. The fit of Model 1B was good: $\chi^2_{(4)} = 3.62$, CFI = 1.00; and RMSEA = .001. Greater presence of the s allele of 5-HTTLPR was associated with greater levels of depressive symptoms, which in turn, related to greater levels of impulsivity. The standardized indirect effect was .074 (Sobel mediation test statistic = 1.82, $p = .034$, one-tailed). The direct association between the presence of s 5HTT allele and impulsivity alone ($\beta = .19$, $p = .068$) became even weaker ($\beta = .11$, $p = .240$) when depression was included in the model as a mediator. The results supported full mediation of the association between 5-HTTLPR and emotional impulsivity by depressive symptoms.

Model 1C examined impulsivity as a potential mediator (Fig. 1c). The fit of Model 1C was also good: $\chi^2_{(5)} = 3.77$, CFI = 1.00; and RMSEA = .001. Greater presence of the s allele of 5-HTTLPR was marginally associated with greater levels of emotional impulsivity, which in turn, related to significantly greater levels of depression. The standardized indirect effect was .059 (Sobel mediation test statistic = 1.56, $p = .059$, one-tailed). The direct association between the presence of the s allele of 5-HTTLPR and depression ($\beta = .20$, $p = .042$) became weaker and non-significant ($\beta = .14$, $p = .140$) when impulsivity was included in the model as a mediator. This result supported partial mediation of the association between the s allele of 5-HTTLPR and depressive symptoms by emotional impulsivity.

Associations of 5-HTTLPR involving facets of depression: exploratory analysis

Further exploratory analyses tested these three models using four facets of depressive symptoms in place of the depressive symptom total. The 20 items of the CES-D form four groups [26, 31]: depressed affect (7 items, $\alpha = .81$ in this sample), lack of positive affect (4 items, $\alpha = .85$), somatic complaints (7 items, $\alpha = .76$), and interpersonal problems (2 items, $\alpha = .53$). The four subscales were significantly intercorrelated ($|.211| < r < |.586|$, $ps < .001$). In these exploratory analyses, the subscale scores jointly replaced the total depressive symptom score.

The fit of Model 1A using these subsets (Fig. 2a) was good: $\chi^2_{(6)} = 10.76$, CFI = .955; and RMSEA = .092. Greater presence of the s allele of 5-HTTLPR was significantly related to elevation of somatic complaints and marginally related to elevated emotional impulsivity, depressed affect, and interpersonal problems.

Model 1B treated depression subscales as joint mediators (Fig. 2b). Greater presence of the *s* allele was significantly related to elevations of both somatic complaints and interpersonal problems and marginally to greater depressed affect. Both depressed affect and interpersonal problems were, in turn, significantly related to greater emotional impulsivity. The standardized indirect effect was .090 (Sobel mediation test statistic = 1.40, $p = .080$, one-tail for the indirect effect of depressed affect; Sobel mediation test statistic = 1.53, $p = .063$, one-tail for the indirect effect of interpersonal problems). These results suggest that depressed affect and interpersonal problems may be pathways by which genotype relates to emotional impulsivity.

Model 1C treated subsets of depressive symptoms as outcomes, with emotional impulsivity as mediator (Fig. 2c). Greater presence of the *s* allele of 5-HTTLPR was marginally associated with elevated emotional impulsivity, which in turn related to significantly greater depressed affect, somatic complaints, and interpersonal problems, and to marginally lower positive affect. The standardized indirect effect for depressed affect was .068 (Sobel mediation test statistic = 1.60, $p = .055$, one-tailed); for somatic complaints was .035 (Sobel mediation test statistic = 1.31, $p = .095$, one-tailed); and for interpersonal problems was .066 (Sobel mediation test statistic = 1.60, $p = .055$, one-tailed). These results suggest that emotional impulsivity may be a partial pathway linking 5-HTTLPR to three facets of depressive symptoms.

In summary, results of these exploratory analyses lent moderate support for the view that depressed affect and interpersonal problems are pathways by which genotype relates to emotional impulsivity, and moderate to weak support for the view that emotional impulsivity is a partial pathway linking 5-HTTLPR to three facets of depressive symptoms.

Discussion

In this sample of women with advanced breast cancer, the short allele of 5-HTTLPR, the serotonin transporter polymorphism, was associated with greater levels of depressive symptoms and also with emotional impulsivity. The findings regarding the polymorphism and depression are consistent with several existing findings (e.g., [14, 15]). The findings regarding the polymorphism and emotion-related impulsivity are also consistent with evidence obtained from nonclinical samples [12, 13]. Importantly, current finding extends the view that low serotonergic function helps promote reactivity to emotion to a new population: advanced cancer patients.

With respect to the possibility that one of the psychological outcomes might be a more important or basic reflection of the serotonin transporter polymorphism than the other, there was some support for mediation in each direction. There was slightly greater support for the view of depressive symptoms (particularly perceptions of social rejection) as mediator, stemming largely from the fact that emotional impulsivity was only marginally related to 5-HTTLPR. These findings need to be replicated with a larger sample before drawing any strong conclusion about mediation.

Nonetheless, the overall pattern does suggest some clinical implications. It is known that cancer patients are less likely to adhere to prescribed treatment regimens when side effects are intense [32–34] and are more likely to make hasty medical decisions when they are overwhelmed and numbed by the distress elicited by the diagnosis of advanced cancer [20, 35, 36]. This implies that sub-groups of advanced cancer patients may be vulnerable to making emotionally charged decisions, which can result in irreversible regret [36–40]. This is an important concern, as the cost and burden to the individual and society can be substantial [41–44]. The findings of this study suggest a genetic contributor to such vulnerabilities and the potential utility of focusing on the discrete aspects of depressive symptoms, especially the perception of interpersonal problems and dejected affect, in future work. Early detection and treatment of depression should be pursued in this vulnerable group [45].

Limitations and conclusion

Limitations of the study include that the measures we used for depressive symptoms and emotional impulsivity were self-reports and not designed for diagnosing clinical depression or impulsivity. We investigated our research questions only with advanced breast cancer patients, without a control group. We examined a single polymorphism but genetic effects on depressive symptoms and emotional impulsivity are certain to be polygenic. Generalizability of the findings is limited by characteristics of participants (female gender, relatively educated, and predominantly non-Hispanic White). Most important is the small sample size, which was underpowered for genetic research and especially detecting indirect effects. The latter in particular should be regarded as suggestive. It will be important to replicate with more diverse and larger populations.

Nonetheless, the study provides the first evidence in a clinically relevant sample—advanced breast cancer patients—that both depressive symptoms and emotion-related impulsivity are partial reflections of low serotonergic function (as indicated by the presence of the s allele of 5-HTTLPR) and perceptions of interpersonal problems are the psychological pathway linking low serotonergic function to emotional impulsivity. The findings thus expand the literature on genetic contributions to both depression and emotion-related impulsivity. In so doing, the findings contribute to our understanding of the genetic basis of two kinds of tendencies that are clinically problematic: depressive symptoms and hyper-reactivity to emotions.

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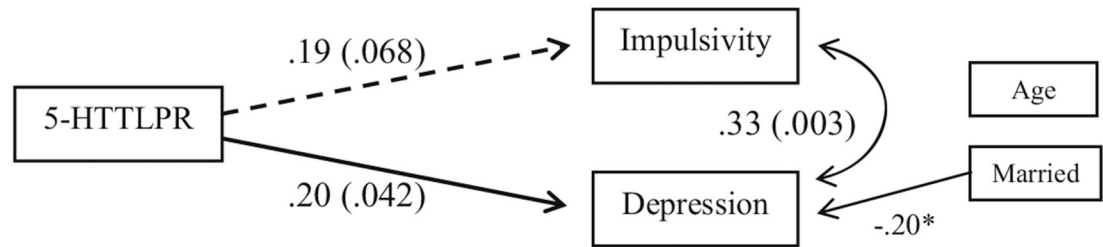
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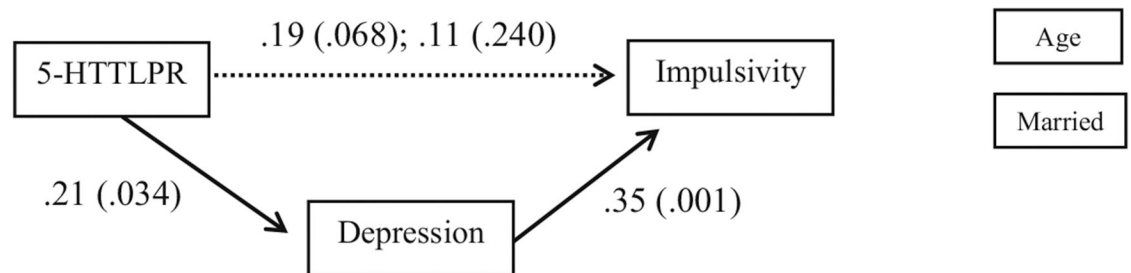
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A. 5-HTTLPR predicting both impulsivity and depressive symptoms simultaneously



B. 5-HTTLPR predicting impulsivity mediated by depressive symptoms



C. 5-HTTLPR predicting depressive symptoms mediated by impulsivity

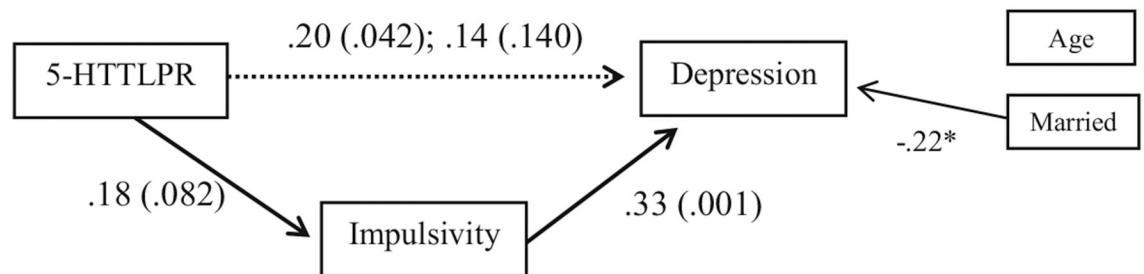


Fig. 1. Testing study models. **a** 5-HTTLPR predicting both impulsivity and depressive symptoms simultaneously. **b** 5-HTTLPR predicting impulsivity mediated by depressive symptoms. **c** 5-HTTLPR predicting depressive symptoms mediated by impulsivity. $n = 95$; $*p < .05$; values outside parentheses are standardized coefficients; inside parentheses are p values; the set of values to the left side of the semicolon are without the proposed mediator in the model; the set of values to the right side of the semicolon are with the proposed mediator in the model; solid paths are significant at $p < .05$; broken paths are marginally significant at $p < .07$; dotted paths or undrawn paths from covariates are not significant, $p > .10$; 5-HTTLPR = 0 for l/l ; 1 for s/l ; and 2 for s/s
 $n = 95$; $*p < .05$; Values outside parenthesis are standardized coefficients, inside parentheses are p values; the set of values to the left side of the semi-colon are without the proposed mediator in the model; the set of values to the right side of the semi-colon are with the proposed mediator in the model; solid paths are significant at $p < .05$; broken paths are

marginally significant at $p < .07$; dotted paths or undrawn paths from covariates are not significant, $p > .10$; 5-HTTLPR = 0 for *l/l*; 1 for *s/l*; and 2 for *s/s*.

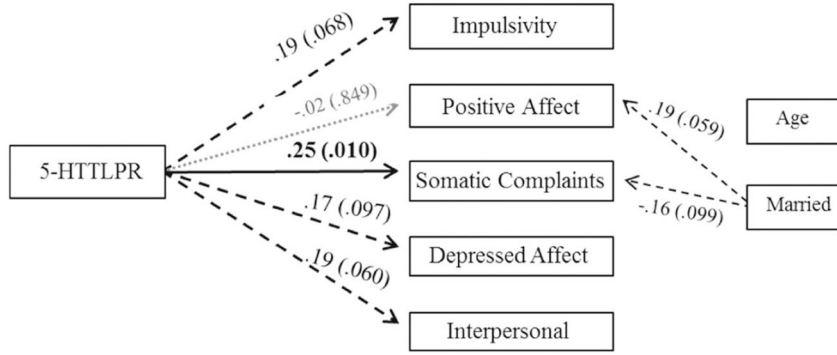
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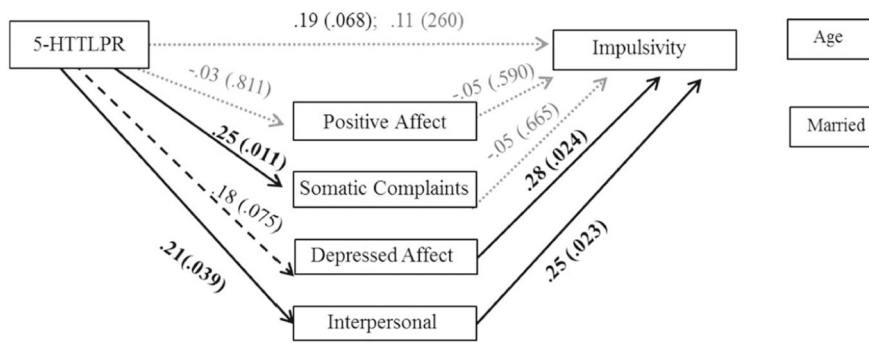
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A. 5-HTTLPR predicting both impulsivity and facets of depressive symptoms



B. 5-HTTLPR predicting impulsivity mediated by facets of depressive symptoms



C. 5-HTTLPR predicting facets of depressive symptoms by impulsivity

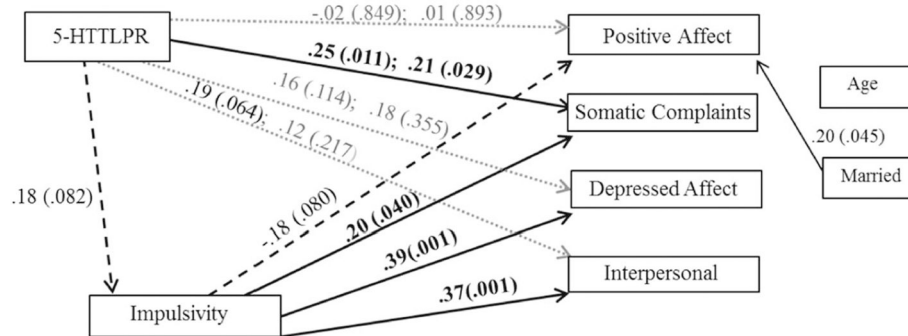


Fig. 2. Testing study models with facets of depressive symptoms. **a** 5-HTTLPR predicting both impulsivity and facets of depressive symptoms. **b** 5-HTTLPR predicting impulsivity mediated by facets of depressive symptoms. **c** 5-HTTLPR predicting facets of depressive symptoms by impulsivity. $n = 95$; $*p < .05$; values outside parentheses are standardized coefficients; inside parentheses are p values; the set of values to the left side of the semicolon are without the proposed mediator in the model; the set of values to the right side of the semicolon are with the proposed mediator in the model; solid paths are significant at $p < .05$; broken paths are marginally significant at $p < .07$; dotted paths or undrawn paths from covariates are not significant, $p > .10$; 5-HTTLPR = 0 for //; 1 for s/t; and 2 for s/s

$n = 95$; * $p < .05$; Values outside parenthesis are standardized coefficients, inside parentheses are p values; the set of values to the left side of the semi-colon are without the proposed mediator in the model; the set of values to the right side of the semi-colon are with the proposed mediator in the model; solid paths are significant at $p < .05$; broken paths are marginally significant at $p < .07$; dotted paths or undrawn paths from covariates are not significant, $p > .10$; 5-HTTLPR = 0 for l/l ; 1 for s/l ; and 2 for s/s .

Table 1Descriptive statistics ($n = 95$)

	Mean or <i>N</i>	SD or %	Scale range
Age	57.67	7.44	45–75 (actual range)
Marital status			
Married	55	57.9	
Separated	4	4.2	
Single/never married	9	9.5	
Divorced	22	23.2	
Widowed	4	4.2	
Other	1	1.1	
Education			
<Some college	40	42.1	
College	18	18.9	
>College	37	39.0	
Ethnicity			
Hispanic or Latino	3	3.2	
Non-Hispanic White	92	96.8	
Serotonin transporter polymorphism (5-HTTLPR) genotype			
<i>s/s</i>	19	20.0	
<i>s/l</i>	48	50.5	
<i>l/l</i>	28	29.5	
Impulsivity	8.66	3.35	6–30
Depression	8.88	7.38	0–60

Table 2

Correlations among study variables

	Age	Married	5-HTTLPR	Impulsivity
Age	–			
Married	.04	–		
5-HTTLPR	–.19 [†]	–.02	–	
Impulsivity	.01	.01	.12	–
Depression	–.09	–.22 [*]	.14	.35 ^{***}

$n = 95$; correlation coefficients among continuous variables (age, impulsivity, and depression) are Pearson correlation coefficients; those with categorical variables (married and 5-HTTLPR) are Spearman correlation coefficients; serotonin transporter polymorphism (5-HTTLPR) genotype = 0 for l/l ; 1 for s/l ; and 2 for s/s

[†]
 $p < .07$;

^{*}
 $p < .05$;

^{***}
 $p < .001$