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Serotonin transporter genotype and mild traumatic brain injury independently influence resilience and perception of limitations in veterans

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ABSTRACT

Evidence indicates that individuals with the 5-HTTLPR variant short/short genotype have increased sensitivity to both positive and negative perceptions of perceived social support. The aim of this study was to evaluate this association among Veterans in the context of mild traumatic brain injury (TBI). As part of a larger TBI center, we performed a cross-sectional study of 67 OEF/OIF/OND Veterans (41 with TBI and 26 controls without TBI) who completed the questionnaires and consented to genetic testing. The primary measures included the Connor-Davidson Resilience Scale (CDRISC) and the Perceived Limitations in community participation subscale of the Community Reintegration of Service Members Instrument (CRIS-PL). Both 5-HTTLPR genotype and TBI status were independently associated with the CRIS-PL ($p = .009$ for genotype, $p = .001$ for TBI) and the CDRISC ($p = .015$ for genotype, $p = .003$ for TBI) scores. This study suggests that both the 5-HTTLPR genotype and TBI status independently, in an almost equal but opposite direction, influence resilience and perceived limitations to social participation. Further, resilience appears more sensitive to perceived limitations in Veterans carrying an S′S′ genotype than in L′ carriers, but only in the context of having sustained a TBI. While having a TBI appeared to increase a Veteran's sensitivity to social stress, the Veteran's who were L′ allele carriers with a TBI fared the worst, with lower resilience and more perceived limitations for community participation compared to L′ carrier Veterans without a TBI or Veterans with the S′S′ genotype regardless of TBI status.

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1. Introduction

The *SLC6A4* (*5-HTT*) gene codes for the serotonin transporter which controls reuptake of serotonin from the synapse into pre-synaptic neurons. Associations between the serotonin transporter and psychiatric illness has been explored for multiple conditions (Wermter et al., 2010) including depression (Caspi et al., 2003; Uher and McGuffin, 2010), posttraumatic stress disorder (Xie et al., 2009), substance abuse (Brody et al., 2009a), anxiety (Stein et al., 2007), and suicidality (Roy et al., 2007). The *5-HTT* gene has also been investigated for its association with resilience.

While there is no single accepted definition of resilience, one definition is "a dynamic process encompassing positive adaptation within the context of significant adversity" (Luthar et al., 2000a), or more simply: why some people do well (Luthar et al., 2000b). Most studies have shown a moderating affect of *5-HTTLPR* on resilience (Amstadter et al., 2012; Markus and De Raedt, 2011; Verschoor and Markus, 2011) emphasizing the long/long genotype compared to the short/short genotype as reflected by 1: a decreased likelihood to quit a challenging activity (Amstadter et al., 2012), 2: increased cognitive-emotional control for L′L′ versus S′S′ (Markus and De Raedt, 2011), and 3: less negative mood changes when exposed to acute stress (Verschoor and Markus, 2011). Other possible mechanisms for the improved long/long genotype resilience may be an attentional bias toward positive affective material (Fox et al., 2009) and/or away from negative word stimuli (Kwang et al., 2010). There is also evidence suggesting the S′ allele's impact on stress-related outcomes may attenuate with increasing age (O'Hara et al., 2012).

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One contrasting study has suggested people with the short/short genotype may have higher resilience and less depression compared to people carrying at least one long allele (Carli et al., 2011). An explanation has been proposed that may account for the disagreement between the long/long and short/short genotypes' association with resilience. Rather than viewing the *5-HTTLPR* allelic variation as a vulnerability gene with the S′ allele conferring more risk than the L′ allele, evidence suggests *5-HTTLPR* actually functions as a plasticity gene moderating the influence of perceived social support on an individual's well-being, with the S′ allele being more sensitive to social valence than the L′ allele (Fox et al., 2011). Current thought is that specific genes may moderate the environment's impact on an individual rather than having a direct link to psychological illness (Caspi and Moffitt, 2006; Fox et al., 2011; Hariri, 2009; Uher, 2009). The associations among *5-HTTLPR* genotype, stress, and the social environment have shown that persons carrying the short allele were more sensitive to positive as well as negative life events (Manuck et al., 2004; Taylor et al., 2006; Way and Taylor, 2010). Taken generally, the *5-HTTLPR* short allele appears to moderate an individual's resilience (i.e., their ability to do well) to their perceived social environment (Brody et al., 2009b; Kaufman et al., 2004; Kilpatrick et al., 2007; Way and Lieberman, 2010).

To our knowledge, no studies have investigated the association between resilience and *5-HTTLPR* genotype in the context of mild traumatic brain injury (TBI). The aim of this study was to evaluate the influence of *5-HTTLPR* genotype on the relationship between resilience and perceived limitations for community participation (adversity) among Operation of Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) Veterans with and without TBI. We first hypothesized that, compared to the non-TBI group, Veterans with TBI will have lower functioning as indicated by a lower resilience and more perceived limitations to community reintegration. Our second hypothesis, based on the plasticity gene theory, was that the *5-HTTLPR* S′S′ genotype will be associated with both greater resilience and fewer perceived limitations than will the L′S′ or L′L′ genotypes. Our third hypothesis was that the genotype effects will vary in an S′ allele dose-dependent manner. Our final hypothesis was that the effects of TBI on resilience and perceived limitations will vary by *5-HTTLPR* genotype.

2. Materials and methods

2.1. Design/participants

This was a cross-sectional pilot study of 67 OEF/OIF/OND Veterans, 41 with mild TBI and 26 controls without any TBI exposure, whose data were collected as part of a larger TBI Center of Excellence. These subjects represent those Veterans enrolled between January 2010 and June 2012 with and without mild TBI who completed the requisite measures and consented to genetic testing.

2.2. Ethical standards

This study was approved by both the local IRB and Veterans Affairs Research & Development Committees. All subjects were consented using approved IRB procedures.

2.3. Conceptual model

Our conceptual model (Fig. 1) emphasizes our outcome of Resilience and the influence of a person's perceived limitations of participation, accounting for the known, and highly inter-correlated, confounding by PTSD, depression, and TBI/post-concussive symptom severity. This model also shows the possible influences by *5-HTTLPR* genotype and TBI.

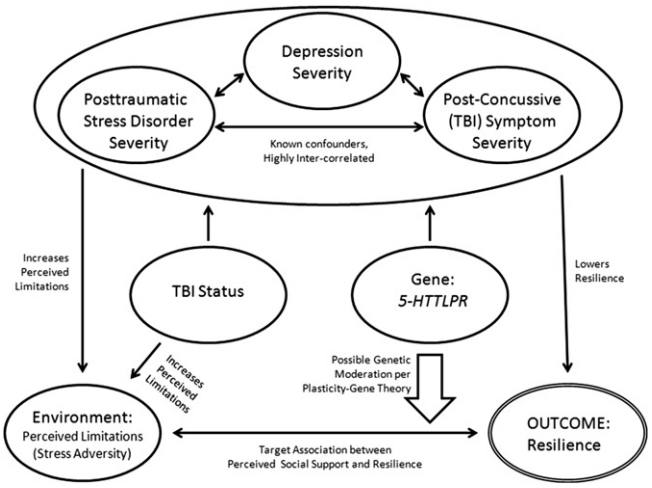

Fig. 1. Conceptual model showing expected interrelationships among the included study variables.

2.4. Measures

2.4.1. Connor-Davidson Resilience Scale (CDRISC)

The CDRISC is a 25-item self-report measure of resilience, or the capability of individuals to cope in the face of major change, adversity, or risk (Connor and Davidson, 2003). Total scores range from 0 to 100, with higher scores indicating higher levels of resilience. This measure has a high internal consistency, Cronbach's $\alpha = .89$, a test-retest reliability intraclass correlation coefficient of .87, and is sensitive to treatment effects (Connor and Davidson, 2003; Davidson et al., 2008; Windle et al., 2011).

2.4.2. Community Reintegration of Service Members Instrument (CRIS)

The CRIS assesses function in community involvement along three dimensions: frequency of participation, perceived limitations in participation, and satisfaction with participation (Resnik et al., 2007, 2009). Construct validity is supported based on comparisons to the SF-36 subscales (Resnik et al., 2009) and response to intervention (Resnik et al., 2011). Subscale total scores range from 1 to 7. Higher scores indicate higher functioning (more participation, fewer perceived limitations, or more satisfaction). We have focused on the perceived limitation subscale (CRIS-PL) as these items evaluate a subject's view of his/her ability to interact in a social environment.

2.4.3. Traumatic brain injury diagnosis

The Clinical Injury Questionnaire (Rehabilitation Care Line, Traumatic Brain Injury Polytrauma Clinic) is an 18-item clinician-administered form adapted from the TBI Comprehensive Evaluation that Veterans Affairs (VA) polytrauma clinics are mandated to use (Belanger et al., 2009). This questionnaire assesses detailed information in a structured format to determine if a patient meets criteria for a history of TBI as defined by the American Congress of Rehabilitation Medicine (ACRM) and the Center for Disease Control and Prevention (CDC) (Menon et al., 2010).

2.4.4. Posttraumatic Symptom Inventory – Civilian (PCL-C)

The PCL is a 17-item self-report measure of the DSM-IV symptoms of PTSD (Weathers et al., 1993; Dobie et al., 2002). The scale has a total score range of 17–85, with higher scores representing increased severity. The PCL has shown good reliability and validity (Lang et al., 2003; Walker et al., 2002).

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2.4.5. Center for Epidemiologic Studies depression Scale (CES-D)

The CES-D is a 20-item scale used to screen for depressive disorder (Radloff, 1977). The CES-D has very good internal consistency (Cronbach alpha of .85–.9) (Roberts and Vernon, 1983). Scores range from 0 to 60, with higher scores reflecting greater levels of depressive symptoms.

2.4.6. Neurobehavioral Symptom Inventory (NBSI)

The Neurobehavioral Symptom Inventory (Cicerone & Kalmar, 1995) is a 22-item scale addressing the cognitive and somatic complaints often seen in brain injury. This is the standard symptom evaluation symptom inventory mandated for use in the VA polytrauma system of care (VHA Directive, 2007-013).

2.5. DNA extraction and genotyping of 5-HTTLPR

Genomic DNA was extracted from approximately 8 mL of whole blood following the Gentra Puregene protocol (Qiagen, Valencia, CA). The promoter region of this gene has either 14 (short) or 16 (long) copies of a 22 base pair repeat polymorphism (*5-HTTLPR*) located 1200 nucleotides upstream of the transcription start site (Lesch et al., 1996; Haddley et al., 2012). The classic long "L" and short "S" alleles (rs4795541) (Lesch et al., 1996) were determined by PCR amplification of DNA to yield a 181 base pair (bp) fragment for the L allele and a 138 bp fragment for the S allele (Hu et al., 2005). An internal variant rs25531 in the L allele, which creates a *Hpa*II restriction site, was genotyped by digestion of the amplified DNA with *Hpa*II (New England Biolabs, Ipswich, MA). The G allele, designated "L_G" (Stein et al., 2006), is digested into 96 and 85 bp fragments, while the A ("L_A") allele remains undigested at 181 bp. The fragment size was determined by electrophoresis in a 4–20% polyacrylamide TBE gel. Since the L_G and S alleles have a lower transcriptional rate than the L_A allele (Hu et al., 2006), the functionally similar L_G and S alleles are designated both as S′ and the L_A allele as L′.

2.6. Power analysis and sample size estimation

Our *a priori* calculations of the required sample size were performed using G-Power 3.1 (Faul et al., 2007, 2009) for the hierarchical linear regression. Our primary analysis will require 68 subjects to be powered to detect a medium effect size ($f^2 = .15$), with an alpha error probability of .05, a power of 80%, two-tailed. Our available sample of 67 subjects was calculated to have an *a priori* power of 79.5%.

2.7. Statistical analyses

Two ANOVAs were used for the evaluation of the continuous demographic variables and the total scores on the *CDRISC*, *CRIS-PL*, *PCL-C*, *CES-D*, and *NBSI*; one for differences by TBI status (presence versus absence), and one for differences by *5-HTTLPR* genotype (S′S′ versus L′S′ versus L′L′) using the Games-Howell multiple pair-wise comparison procedure to account for differences in sample sizes and variances among the three genotypes. One Mann–Whitney *U* test was used to evaluate categorical demographic variables by TBI status, and one Kruskal–Wallis test was used to evaluate the categorical demographic variables by *5-HTTLPR* genotype.

Because the L′S′ and L′L′ genotypes both differed from the S′S′ genotype but did not differ from each other on both the *CDRISC* ($p = .717$) and *CRIS-PL* ($p = .826$), the decision was made to collapse the L′S′ and L′L′ genotypes into a single group, L′ carrier, in subsequent analyses. A third ANOVA was used to evaluate for differences in the total scores on the *CDRISC* and *CRIS-PL* for combined genotype groups (S′S′ versus L′ carrier) by TBI status.

Lastly, a hierarchical regression (hierarchical levels noted as per Woltman et al., 2012) was used to test for moderation of the association between the *CRIS-PL* score (Level-1) and the *CDRISC* score (level-1) by TBI status (level-2) and by *5-HTTLPR* genotype status (S′S′ versus L′ carrier) (level-2). As previously reported (Foa et al., 1997; Iverson, 2006), the severity scores for PTSD, depression, and post-concussive symptoms were highly inter-correlated (*PCL-C* and *CES-D*: $r^2 = .854$, *PCL-C* and *NBSI*: $r^2 = .917$, and *CES-D* and *NBSI*: $r^2 = .813$; all $p < .001$). We therefore ran a principal component analysis that resulted in a single co-morbidity factor (level-1) used to control for these co-morbidities in the regression. Exploratory analysis for differences in the regression line-of-best fit slopes was performed via multiple *T*-Tests.

P-values were corrected experiment-wise for the six planned comparisons to account for the increased risk of Type 1 error, resulting in a Bonferroni correction for multiple testing with a new $p \leq .008$. SPSS version 15 for Windows (IBM) was used for these analyses.

2.8. Hardy–Weinberg equilibrium

Hardy–Weinberg equilibrium was not violated for the genotype *5-HTTLPR* (rs25531) S′ and L′ allele frequencies for both the TBI ($p = .917$) and non-TBI ($p = .500$) groups, or for the overall combined sample ($p = .882$).

3. Results

3.1. Demographics: mild TBI versus Non-TBI controls

We evaluated the mild TBI and non-TBI groups for differences in demographics (Table 1). Male veterans reported having sustained a TBI more often than female veterans ($p = .001$). As expected, the number of reported blast exposures differed by group, with those in the mild TBI group reporting a mean of 5.5 exposures (median = 2.0, mode = 1.0, range = 0 to 57 where two of the 41 TBI subjects had only non-blast related TBI) while those in the non-TBI group reported no exposures ($p = .011$).

3.2. Primary and co-morbidity measures: mild TBI versus non-TBI controls

We examined primary and co-morbidity measures for differences due to TBI status in Table 1. Differences were noted for all primary and co-morbidity measures. Compared to subjects without a TBI, subject's with a TBI had lower *CDRISC* scores ($p = .003$), lower *CRIS-PL* scores ($p = .001$), higher *PCL-C* scores ($p < .001$), higher *CES-D* scores ($p = .001$), and higher *NBSI* scores ($p < .001$).

3.3. Demographics: number of 5-HTTLPR S′ alleles

Subjects were grouped according to their *5-HTTLPR* genotype in Table 2. No differences were noted among the S′S′, L′L′ and L′S′ groups for any of the demographic variables (all $p > .05$).

3.4. Primary and co-morbidity measures: 5-HTTLPR genotype

We evaluated whether there was an effect of the *5-HTTLPR* on resilience, the *CRIS-PL*, and on the co-morbid severity scores for PTSD, depression, and TBI symptom severity as reported in Table 2. The *CDRISC* score initially trended toward a significant association with *5-HTTLPR* genotype ($p = .009$) with the S′S′ genotype group scoring higher than the L′L′ group ($p = .001$) and from the L′S′ group ($p = .003$); the L′L′ and L′S′ groups did not differ from each other ($p = .717$). When subsequently grouped as S′S′ versus the L′ carrier

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Table 1
Demographics and measurement scales by TBI diagnostic status.

Variable	*n*	TBI	*n*	Non-TBI	*p*-Value
		Mean (SD) or %		Mean (SD) or %	
Age (SD)	40	31.8 (7.6)	26	33.2 (9.1)	= .489
Male	41	95.1%	26	61.5%	= .001**
Race	41		26		= .824
African-American	12	29.3%	6	23.1%	
Caucasian	28	68.3%	18	69.2%	
Other	1	2.4%	2	7.7%	
Ethnicity	41		26		= .435
Non-hispanic	30	73.2%	17	64.0%	
Hispanic	11	26.8%	9	36.0%	
Marital status	40		26		= .094
Single	10	25.0%	11	42.3%	
Married	16	40.0%	10	38.5%	
Other	14	35.0%	5	19.2%	
Years education (SD)	41	14.0 (2.0)	26	14.3 (1.9)	= .521
Military branch	41		26		= .152
Army	27	65.9%	11	44.0%	
Navy	5	12.2%	7	28.0%	
Air force	2	4.9%	2	8.0%	
Marines	6	14.6%	4	16.0%	
Other/multiple	1	2.4%	1	4.0%	
5-HTTLPR genotype	41		26		= .317
L′L′	14	34.1%	8	30.8%	
L′S′	21	51.2%	10	38.5%	
S′S′	6	14.6%	8	30.8%	
# Deployments (SD)	40	1.8 (1.0)	26	1.8 (1.1)	= .976
# Days since TBI (SD)	40	1557.2 (729.4)	0	–	–
# Blast exposures (SD)	40	5.5 (10.1)	24	–	= .011*
Loss of consciousness	36		0		–
< 30 min	35	97.2%	–	–	
30 min to 24 h	1	2.8%	–	–	
> 24 h	0	.0%	–	–	
Posttraumatic amnesia	39		0		–
< 1 h	26	66.7%	–	–	
1–24 h	8	20.5%	–	–	
> 24 h	5	12.8%	–	–	
CDRISC[a] total score	41	60.6 (24.3)	26	77.7 (18.8)	= .003**
CRIS-PL[b]	41	4.9 (1.0)	26	5.7 (.9)	= .001**
PCL-C[c] total score	41	54.6 (16.4)	26	28.6 (11.1)	<.001**
CES-D[d] total score	41	26.6 (15.4)	26	13.9 (11.0)	= .001**
NBSI[e] total score	41	39.7 (19.3)	26	15.1 (13.5)	<.001**

*$p \leq .05$, but not meeting Bonferroni Correction at $p \leq .008$.
**Meeting Bonferroni Correction at $p \leq .008$.
[a] CDRISC: Connor-Davidson Resilience Scale. Higher scores represent higher resilience.
[b] CRIS-PL: Community Reintegration of Service Members Instrument – Perceived Limitations Scale. Higher scores represent fewer perceived limitations.
[c] PCL-C: Posttraumatic Symptom Inventory – Civilian. Higher scores represent more PTSD symptoms.
[d] CES-D: Center for Epidemiologic Studies Depression Scale. Higher scores represent more depressive symptoms.
[e] NBSI: Neurobehavioral Symptom Inventory. Higher scores represent more post-concussive/TBI symptoms.

genotypes, the *CDRISC* showed higher scores ($p = .003$) for the S′S′ genotype (mean 83.5, SD = 10.7) than for the L′ carrier genotype (mean 62.9, SD = 24.4).

Results for the effects of *5-HTTLPR* on the *CRIS-PL* scale showed a trend toward significance ($p = .015$), but did not meet Bonferroni criteria of $p \leq .008$. In particular (not shown in Table 2), the S′S′ genotype group differed from the L′L′ group ($p = .008$), but only trended differently from the L′S′ group ($p = .025$), while the L′L′ and L′S′ groups did not differ from each other ($p = .826$). When subsequently grouped as S′S′ versus the L′ carrier genotypes, the *CRIS-PL* showed higher scores ($p = .004$) for the S′S′ genotype (mean 5.9, SD = .8) than for the L′ carrier genotypes (mean 5.0, SD = 1.0).

Regarding the three co-morbidity rating scales, the total scores for the *PCL-C*, the *CES-D*, and the *NBSI* all trended toward significance with the S′S′ scoring lower on all three measures than the L′L′ or L′S′ genotypes (for three genotype groups all *p-values* were between .03 and .06; as S′S′ versus L′ carrier all *p-values* were between .011 and .021, none meeting Bonferroni criteria of $p \leq .008$).

3.5. Relationship between 5-HTTLPR genotype, TBI status, CDRISC, and CRIS-PL

We evaluated the association between the *CDRISC* and *CRIS-PL* scores for affects by combined genotype and TBI diagnosis grouping variable: S′S′ with TBI, S′S′ without TBI, L′ carrier with TBI, and L′ carrier without TBI. The model was significant for both the *CDRISC* and for the *CRIS-PL* at $p \leq .001$ (Table 3). Upon finding a significant genotype by TBI status interaction for both the *CDRISC* ((2,64) $F = 9.126$, $p < .001$) and the *CRIS-PL* ((2,64) $F = 9.921$, $p < .001$), the subsequent subgroup analyses revealed, for the *CDRISC*, the L′ carrier TBI group differed from all three other groups, which did not differ from each other. For the *CRIS-PL*, the L′ carrier TBI group differed only from the L′ carrier non-TBI and the S′S′ non-TBI groups, but did not differ from the S′S′ TBI group.

Fig. 2 graphs the genotype by TBI status' effect on the relationship between the *CRIS-PL* and the *CDRISC*. The two important points regarding the slopes of the line-of-best-fit for the groups associations between the *CDRISC* and the *CRIS-PL* are as follows. 1: At low perceived limitations, all subjects reported high resilience (i.e., doing well) regardless of genotype or TBI status. 2: The slope (SD), defined as the change in *CDRISC* for a 1 point change in *CRIS-PL*, for each group is as follows: S′S′ with TBI = 15.4 (3.6), S′S′ without TBI = 6.6 (2.9), L′ carrier with TBI = 18.3 (3.0), and L′ carrier without TBI = 13.3 (4.6). The L′ carrier with TBI group differed from the S′S′ without TBI group ((4,39) $T = 2.778$, $p = .008$, meeting Bonferroni criteria), while the S′S′ without TBI group was trending different from the S′S′ with TBI group ((4,10) $T = 2.441$, $p = .035$, not meeting Bonferroni criteria). All other group comparisons were not significantly different (all $p > .230$). For more general reference, the slopes of the larger group comparisons were: L′ carrier = 17.3 (2.3), S′S′ = 9.9 (2.4); and No TBI = 12.0 (3.4), TBI = 19.0 (2.5). A trend was found between the L′ carrier versus S′S′ groups ((3,64) $T = 2.220$, $p = .030$), while the No TBI versus TBI groups did not reach statistical significance ((3,64) $T = 1.680$, $p = .098$).

Overall, resilience appears more sensitive to perceived limitations in L′ carrier Veterans than in those with the S′S′ genotype, and the presence of TBI may increase an individuals′ sensitivity to social environmental influences as measured by resilience.

3.6. Association of genotype, TBI status, CRIS-PL, and CDRISC

A hierarchical linear regression was used to evaluate the relative influences of *5-HTTLPR* genotype, TBI status, and the *CRIS-PL* on the *CDRISC* (the final 7-step model is reported in Tables 4 and 5). The TBI status and *5-HTTLPR* genotype groups both showed a mild direct effect on resilience (model steps one and two), while the genotype by TBI status interaction term included in step 3 was non-significant at $p = .179$. The addition of the mental health co-morbidity factor was highly significant ($p < .001$) and overwhelmed the influences of TBI or genotype. The *CRIS-PL* subscale was also significant even after controlling for the influences of PTSD, depression, and TBI symptoms severity using the co-morbidity factor variable. The interaction terms for genotype with the co-morbidity factor and for genotype and TBI status by *CRIS-PL* were non-significant.

4. Discussion

This study evaluated if *5-HTTLPR* genotype influenced resilience and perceived limitations to social participation in OEF/OIF/OND Veterans with and without TBI. Our first hypothesis that the

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Table 2
Demographics and measurement scales by *Serotonin Transporter* genotype.

Variable	Total *n*	L′L′	Total *n*	L′S′	Total *n*	S′S′	*P*-Value
Age (SD)	22	32.4 (6.1)	30	33.3 (10.0)	14	30.3 (6.9)	= .551
Male	22	72.7%	31	83.9%	14	92.9%	= .294
Race	22		31		14		= .725
African-American	6	27.3%	8	25.8%	4	28.6%	
Caucasian	16	72.7%	22	71.0%	8	57.1%	
Other	0	.0%	1	3.2%	2	14.3%	
Ethnicity	21		31		14		= .663
Non-hispanic	16	76.2%	20	64.5%	10	71.4%	
Hispanic	5	23.8%	11	35.5%	4	28.6%	
Marital status	22		30		14		= .611
Single	8	36.4%	8	26.7%	5	35.7%	
Married	5	22.7%	14	46.7%	7	50.0%	
Other	9	40.9%	8	26.7%	2	14.3%	
Years education (SD)	22	14.7 (2.5)	31	13.7 (1.8)	14	14.1 (1.3)	= .194
Military branch	22		31		13		= .142
Army	11	50.0%	21	67.7%	6	46.2%	
Navy	6	27.3%	5	16.1%	1	7.7%	
Air Force	2	9.1%	2	6.5%	0	.0%	
Marines	2	9.1%	3	9.7%	5	38.5%	
Other/multiple	1	4.5%	0	.0%	1	7.7%	
# Deployments (SD)	21	1.6 (1.0)	31	2.0 (1.0)	14	1.7 (1.0)	= .308
TBI diagnosis	22	63.6%	31	67.7%	14	42.9%	= .278
# Blast exposures (SD)	20	1.5 (1.8)	30	5.1 (11.2)	14	2.8 (6.7)	= .325
# Days since TBI (SD)	13	1585.7 (613.5)	22	1444.4 (798.0)	6	1871.3 (637.0)	= .439
Loss of consciousness	12		18		6		= .368
< 30 min	11	91.7%	18	100.0%	6	100.0%	
30 min to 24 h	1	8.3%	0	.0%	0	.0%	
> 24 h	0	.0%	0	.0%	0	.0%	
Posttraumatic amnesia	13		20		6		= .490
< 1 h	9	69.2%	14	70.0%	3	50.0%	
1–24 h	4	30.8%	3	15.0%	1	16.7%	
> 24 h	0	.0%	3	15.0%	2	33.3%	
CDRISC[a] total score	22	59.8 (24.9)	31	65.1 (24.3)	14	83.5 (10.7)	= .009*
CRIS-PL[b]	22	4.9 (1.0)	31	5.1 (1.1)	14	5.9 (.8)	= .015*
PCL-C[c] total score	22	46.7 (20.7)	31	48.1 (18.7)	14	33.0 (14.7)	= .040*
CES-D[d] total score	22	25.5 (17.2)	31	22.7 (14.6)	14	13.4 (9.6)	= .057
NBSI[e] total score	22	34.9 (20.9)	31	32.4 (21.0)	14	17.6 (16.9)	= .037*

*: $p \leq .05$, but not meeting Bonferroni Correction at $p \leq .008$.
[a] CDRISC: Connor-Davidson Resilience Scale. Higher scores represent higher resilience.
[b] CRIS-PL: Community Reintegration of Service Members Instrument – Perceived Limitations Scale. Higher scores represent fewer perceived limitations.
[c] PCL-C: Posttraumatic Symptom Inventory – Civilian. Higher scores represent more PTSD symptoms.
[d] CES-D: Center for Epidemiologic Studies Depression Scale. Higher scores represent more depressive symptoms.
[e] NBSI: Neurobehavioral Symptom Inventory. Higher scores represent more post-concussive/TBI symptoms.

presence of a TBI would be associated with lower resilience and more perceived social limitations was supported. Our second hypothesis that the S′S′ genotype would be associated with more resilience in the context of fewer perceived limitations when compared to the L′S′, or L′L′ genotypes was also supported. Our third hypothesis was not supported in that there was not a dose related effect of the S′ allele, with the genotype effects rather grouping as S′S′ versus L′ carrier. Our fourth hypothesis was supported in part, with both TBI status and *5-HTTLPR* genotype both showing a very mild moderating effect on the relationship between resilience and perceived support. However, we were not expecting TBI status and S′S′ genotype to have influences that were almost equal, independent, and in opposite directions (standardized β for TBI was .298 and for TBI was −.297). Therefore, having either a TBI or being a *5-HTTLPR* L′ carrier is associated with lower resilience and more perceived limitation for participation, but the two factors do not themselves interact. This results in an additive affect, with the L′ carrier Veterans with a TBI having the lowest resilience and most perceived limitations.

Table 3
Association of *Serotonin Transporter* genotype by TBI status for the *CDRISC* score and the *CRIS-PL* score.

Group	Total *n*	CDRISC[a]	Total *n*	CRIS-PL[b]
A. L′ carrier without TBI[c]	18	75.0 (21.6)	18	5.6 (.9)
B. L′ carrier with TBI[c]	35	56.7 (23.7)	35	4.7 (.9)
C. S′S′ genotype without TBI[c]	8	83.8 (8.5)	8	6.0 (.9)
D. S′S′ genotype with TBI[c]	6	83.2 (14.1)	6	5.8 (.8)
Overall model *p*-value		=.001		<.001
Pair-wise comparisons		B < A*,C**,D*		B < A*,C*

*$p \leq .05$, but not meeting Bonferroni Correction at $p \leq .008$.
**Meeting Bonferroni Correction at $p \leq .008$.
[a] CDRISC: Connor-Davidson Resilience Scale Total Score. Higher scores represent higher resilience.
[b] CRIS-PL: Community Reintegration of Service Members Instrument Perceived Limitation Subscale Total Score. Higher scores represent fewer perceived limitations.
[c] TBI: Traumatic Brain Injury.

Our findings support Fox and colleagues' (2011) conceptualization of *5-HTTLPR* as a plasticity gene and serves to extend this consideration to a population of OEF/OIF/OND Veterans irrespective of their TBI status. Our results were consistent with the literature in that the *5-HTTLPR* genotype showed only a very mild direct influence on both resilience and perceived limitations, thereby supporting the view that *5-HTTLPR's* effects are most likely secondary to the more direct effects of the social environment (Caspi and Moffitt, 2006; Hariri, 2009; Uher, 2009). While our results showed that Veterans with TBI carrying the S′S′ genotype had less change in resilience for each unit change in perceived limitations

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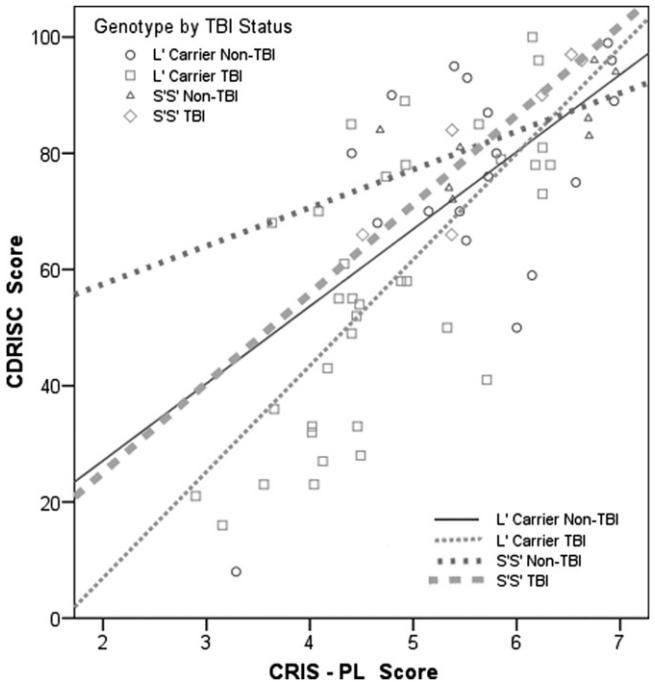

Fig. 2. Moderation of the association between the Connor-Davidson resilience scale (CDRISC) score and the community reintegration of Service members Instrument – perceived limitation (CRIS-PL) subscale score by *5-HTTLPR* S′S′ versus L′ carrier genotypes and by TBI status.

compared to Veterans with TBI carrying at least one L′ allele, all subject's with low perceived limitations had high resilience regardless of genotype or TBI status. This supports the majority of the previous serotonin-based resilience studies with the long/long genotype being associated with high resilience and fewer perceived limitations (Amstadter et al., 2012; Fox et al., 2009; Kwang et al., 2010; Markus and De Raedt, 2011; Verschoor and Markus, 2011).

Multiple issues may contribute to our not showing resilience in persons with S′S′ genotype as being more sensitive than L′ carriers to their perceived social environment. First, our S′S′ genotype group had higher resilience scores and a smaller range of scores on our measure of the perceived social environment than the L′ carrier groups. It is interesting to note that none of the S′S′ subjects had a poor score on either the *CDRISC* or the *CRIS-PL. W*hile the generally higher scores, both indicating higher functioning, for the S′S′ group support the hypothesis that the S′ allele is responsive to positive social valence, we cannot comment on their association with negative social valence. A second possible explanation may relate to sample differences between ours and prior studies. None of the other six resilience studies focusing on serotonin genetics used Veterans; rather they focused on early adolescents (Amstadter et al., 2012), healthy college students (Fox et al., 2009, 2011; Kwang et al., 2010; Markus and De Raedt, 2011), or prisoners (Carli et al., 2011). Our use of Veterans with and without a diagnosis of TBI suggests that the presence of TBI increases a person's sensitivity to social valence irrespective of *5-HTTLPR* genotype.

Only one study had also used the CDRISC as a measure of resilience (Carli et al., 2011). The others were all active enrollment studies, many with pre-post data available for evaluating acute changes, that employed observed measures of response to negative stimuli (Amstadter et al., 2012; Fox et al., 2009, 2011; Kwang et al., 2010; Markus and DeRaedt, 2011). Since we did not have a directed task associated with acutely increased stress, we may have missed the hypothesized finding of an association between the S′ allele and perceived duress.

Table 4
Mild moderating effects by *5-HTTLPR* genotype and by TBI status on the association between the perceived limitations for social reintegration (CRIS-PL) score and the Connor-Davidson resilience scale (CDRISC) score, prior to controlling for the co-morbid severity of PTSD, depression, and TBI symptoms.

Step	Model	Standardized	
		β	*p*-Value*
1	*5-HTTLPR* genotype[a]	.355	.003
2	*5-HTTLPR* genotype[a]	.298	.011
	TBI Status[b]	−.297	.011
3	*5-HTTLPR* genotype[a]	.151	.337
	TBI status[b]	−.379	.004
	Genotype[a] by TBI status[b] interaction	.215	.179
4	*5-HTTLPR* genotype[a]	.023	.854
	TBI status[b]	.015	.896
	Genotype[a] by TBI Status[b] Interaction	.184	.138
	Co-morbidity factor[c]	−.711	<.001
5	*5-HTTLPR* genotype[a]	.106	.593
	TBI status[b]	.025	.831
	Genotype[a] by TBI status[b] interaction	.125	.450
	Co-morbidity factor[c]	−.729	<.001
	Genotype[a] by TBI Co-morbidity factor[c] interaction	.084	.591
6	*5-HTTLPR* genotype[a]	.154	.402
	TBI status[b]	.016	.883
	Genotype[a] by TBI status[b] interaction	.020	.896
	Co-morbidity factor[c]	−.366	.017
	Genotype[a] by TBI Co-morbidity factor[c] interaction	.136	.350
	CRIS-PL[d]	.464	.001
7	(Constant)	–	.334
	5-HTTLPR genotype[a]	.202	.783
	TBI status[b]	−.451	.387
	Genotype[a] by TBI status[b] interaction	−.008	.963
	Co-morbidity factor[c]	−.331	.043
	Genotype[a] by TBI Co-morbidity factor[c] interaction	.125	.554
	CRIS-PL[d]	.374	.053
	Genotype[a] by CRIS-PL[d] interaction	.445	.360
	TBI Status[b] By CRIS-PL[d] interaction	−.039	.964

* Hierarchical Linear Regression.
Dependent Variable: Connor-Davidson Resilience Scale (CDRISC) score.
[a] *5-HTTLPR* Genotype: coded as 0 = L′ carrier, 1 = S′S′.
[b] TBI Status: coded as 0 = no Traumatic Brain Injury (TBI), 1 = with TBI.
[c] Co-Morbidity Factor is the single derived factor score accounting for the high inter-correlation between the PCL-C total score, CES-D total score, and NBSI total score.
[d] Community Reintegration of Service Members Instrument – Perceived Limitations in Community Reintegration subscale.

The relevance of this analysis to TBI and to our growing understanding of the relationship between the *5-HTTLPR* genotype and the impact of social valence are two-fold. First, experts have speculated that due to the reported difficulties with memory, concentration, and other cognitive symptoms, Veterans with TBI may require modifications to existing evidence-supported treatments for conditions such as PTSD, depression, substance abuse and pain (Lew et al., 2009). Our results suggest that all Veterans, regardless of *5-HTTLPR* genotype or TBI status, may still be responsive to those interventions that include a strong social support component, thereby supporting prior suggestions that a supportive social environment may provide greater therapeutic effects (Fox et al., 2011).

Second, Veterans and family members attribute neurobehavioral changes and deficits in the Veteran's executive functioning, such as with impulse or anger control issues, to TBI. These post-concussive symptoms could mask or overwhelm the association between *5-HTTLPR* S′S′ genotype and social valence (Halbauer et al., 2009). Our results suggest this contention is true in that TBI status was independent of *5-HTTLPR*'s influence, but our results also suggest that TBI-related changes may blunt the association between perceived limitations and resilience as TBI and *5-HTTLPR* S′S′ genotype

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Table 5
Final seven-step regression model summary.

Step	Variable added into model	Adjusted R^2	R^2 change (p-value)	F (d.f.)	Model p-value
1	*5-HTTLPR* genotype[a]	= .113	= .003**	(1,65) = 9.385	= .003**
2	TBI status[b]	= .186	= .011*	(2,64) = 8.549	= .001**
3	Genotype[a] by TBI status[b] interaction	= .197	= .179	(3,63) = 6.390	= .001**
4	Co-morbidity factor[c]	= .519	<.001**	(4,62) = 18.817	<.001**
5	Genotype[a] by Co-morbidity factor[c] interaction	= .514	= .591	(5,61) = 14.940	<.001**
6	CRIS-PL[d]	= .587	= .001**	(6,60) = 16.615	<.001**
7	Genotype[a] by CRIS-PL[d] interaction TBI status[b] by CRIS-PL[d] interaction	= .579	= .634	(8,58) = 12.352	<.001**

*$p < .05$ but not meeting Bonferroni Correction of $p \leq .008$.
**$p \leq .008$, meeting Bonferroni Correction.
[a] *5-HTTLPR* Genotype: coded as 0 = L′ carrier, 1 = S′S′.
[b] TBI Status: coded as 0 = no Traumatic Brain Injury (TBI), 1 = with TBI.
[c] Co-Morbidity Factor is the single derived factor score accounting for the high inter-correlation between the PCL-C total score, CES-D total score, and NBSI total score.
[d] Community Reintegration of Service Members Instrument – Perceived Limitations in Community Reintegration subscale.

influence both resilience and perceived limitations in almost equal but opposite directions. Therefore, TBI-related changes may be contributing through non-*5-HTTLPR*-related mechanisms to influence impulse control, depression, and other relevant behaviors.

There are several limitations to our conclusions. As a cross-sectional study, no causality can be inferred. Future studies would benefit from using a prospective design to allow for causality of social influences (negative and positive) on resilience and general functioning, and obtaining larger sample sizes, which would provide greater power for assessing covariates. These findings should be considered preliminary, and the generalizability of results may be limited to the population of male OEF/OIF/OND Veterans with and without mild blast-related TBI. Further studies will be needed to examine if these findings can be replicated in other populations, including a broader selection of TBI mechanisms and with a larger sample of female Veterans. Additionally, we acknowledge limitations in our approach to detailing TBI information using the Clinical Injury Questionnaire which may include problems such as the fallibility of memory and the difficulties of distinguishing between altered mental status due to overwhelming psychological stress and concussion.

In conclusion, this pilot study has found evidence suggesting that both the *5-HTTLPR* S′S′ genotype and TBI status independently are associated, in an almost equal but opposite direction, with both resilience and perceived limitations to social participation. Veteran's who were L′ allele carriers with a TBI fared the worst, with lower mean resilience compared to L′ carrier Veterans without a TBI or Veterans with the S′S′ genotype regardless of TBI status.

Contributors

Dr. Graham was responsible for the statistical analyses and writing the first draft of this manuscript. Dr. Helmer was responsible for the data collection and assisted in the design of the study. Dr. Petersen assisted with the conceptual model and statistical analyses. Drs. Kosten and Nielsen assisted with the conceptual design of the study. Dr. Nielsen and Mr. Harding oversaw the genetics of the study. All authors made written contributions and approved the final manuscript.

Conflict of interest

No competing financial interests exist. The authors have full control over the data used in the preparation of this manuscript.

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