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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.

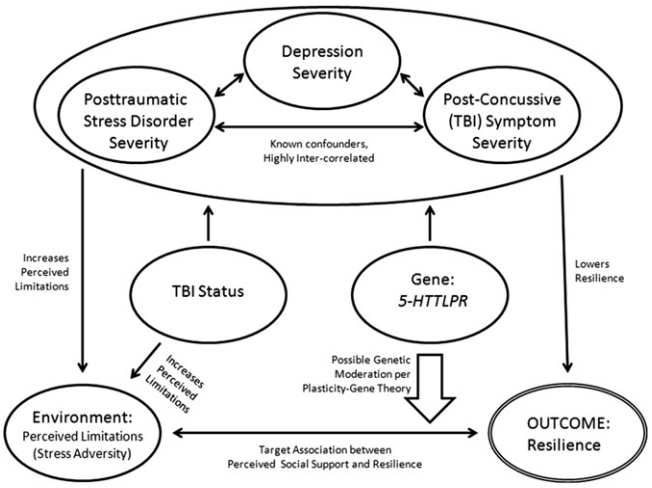

Fig. 1. Conceptual model showing expected interrelationships among the included study variables.

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).