Role of the Serotonin Transporter Gene in Resilience to Stress and Trauma: An Integrative Review

Kosuke Niitsu

University of Nebraska Medical Center, KosukeNiitsu@gmail.com
Role of the Serotonin Transporter Gene in Resilience to Stress and Trauma: An Integrative Review

Kosuke Niitsu, MSN, APRN-NP, PMHNP-BC
UNMC College of Nursing, PhD Program

Background
- Most people are exposed to potentially traumatic events at some point in their lives, but many are surprisingly resilient.
- Resilience is a complex multi-dimensional construct.
- The heritability of resilience is .38 - .52 among US adults.
- Resilience is polygenic with at least 9 candidate genes.
- Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR) is of increasing clinical interest.

Serotonin Transporter Gene

Results
- 26 articles met all criteria
- 17 of 26 (65%) studies found that the individuals who carry the S allele of 5-HTTLPR were less resilient to stress and trauma
- 4 of 26 (15%) studies found those who carry the S allele of 5-HTTLPR were more resilient
- The remaining 5 publications (20%) did not find any differences in resilience between those with L or S alleles

Discussion & Conclusion
- The hypothesis is partially supported by the analysis because the majority of the studies (17/26, 65%) found that S allele carriers are less resilient.
- Nevertheless, 4/26 (15%) of the studies found that S allele carriers are more resilient and 5/26 (20%) found no statistically significant association between 5-HTTLPR and resilience.
- 3 dimensions of the articles may explain the inconsistent results.
- 1) Definition of resilience
- No single agreed-upon definition of resilience.
- Emergent resilience represents trajectories of positive adjustment in the context of chronically stressful circumstances.
- Minimal-impact resilience is applied in the context of minimal-impact and chronic stressful circumstances.
- Future studies should more clearly conceptualize and operationalize resilience, genotype rs25531, and investigate the environment in a full range in order to address the differential susceptibility.

Hypothesis
- Little is known about whether individuals who carry the S allele of 5-HTTLPR are less resilient to stress and trauma compared to L allele carriers.
- Because evidence indicates that S allele carriers are at increased risk of psychopathology such as PTSD, it is hypothesized that S allele carriers are less resilient to stress and trauma compared to L allele carriers.

Methods
- PubMed, EMBASE, PsychINFO, and CINAHL databases were searched.
- Keywords: “serotonin transporter gene”, “5-HTTLPR”, “resilience”.
- Inclusion criteria for the articles reviewed: (1) human subjects approved research, (2) published in English, (3) peer-reviewed research articles, (4) both 5-HTTLPR and resilience measured.
- The results of the literature search were analyzed and summarized in Table.

<table>
<thead>
<tr>
<th>Stressor / Trauma Measure</th>
<th>Resilience Measure</th>
<th>Sample</th>
<th>Finding (Less resilient)</th>
<th>rs25531?</th>
<th>Authors (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood maltreatment</td>
<td>Children’s Depression Inventory</td>
<td>Unmedicated Crowds</td>
<td>L</td>
<td>No</td>
<td>Breyer et al. (2013)[18]</td>
</tr>
<tr>
<td>Maladaptive behavior</td>
<td>Resilient functioning</td>
<td>Unmedicated</td>
<td>L</td>
<td>No</td>
<td>Cicchetti &amp; Ragozin (2012)[12]</td>
</tr>
<tr>
<td>Childhood maltreatment</td>
<td>Youth Self-Report (depression/anxiety and somatic symptoms)</td>
<td>Unmedicated</td>
<td>S</td>
<td>No</td>
<td>Cicchetti &amp; et al. (2007)[47]</td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>Connor-Davidson Resilience Scale (CD-RISC)</td>
<td>Male prisoners</td>
<td>L</td>
<td>No</td>
<td>Cari et al. (2011)[17]</td>
</tr>
<tr>
<td>Childhood adversity</td>
<td>Early Adolescent Temperament Questionnaire-Revised (EATQ-R)</td>
<td>Dutch adolescents</td>
<td>S</td>
<td>Yes</td>
<td>Nederfelt et al. (2010)[20]</td>
</tr>
<tr>
<td>Distal Adverse Childhood Events</td>
<td>Zung Self-Rating Depression Scale: (CD-RISC as ‘Tarfett’)</td>
<td>General population</td>
<td>S</td>
<td>Yes</td>
<td>Shepely et al. (2013)[12]</td>
</tr>
<tr>
<td>Childhood Trauma Questionnaire</td>
<td>CDRISC-10</td>
<td>Undergraduate students</td>
<td>S</td>
<td>Yes</td>
<td>Stein et al. (2009)[16]</td>
</tr>
<tr>
<td>Additional Trauma</td>
<td>Davidson Trauma Scale (A CD-RISC)</td>
<td>Individuals from the Detroit Neighborhood Health Study</td>
<td>L</td>
<td>No</td>
<td>Hemmings et al. (2013)[16]</td>
</tr>
<tr>
<td>Life Events Checklist</td>
<td>PTSD Checklist</td>
<td>Not Significant (NS)</td>
<td>No</td>
<td>No</td>
<td>Koene et al. (2011)[12]</td>
</tr>
<tr>
<td>Perceived Risk</td>
<td>Schedule of Racial Events (perceived racial discrimination)</td>
<td>Conduct problems</td>
<td>African American youths</td>
<td>S</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Schedule of Racial Events (perceived racial discrimination)</td>
<td>Physical health, mental health, trouble with the law, &amp; social relationships</td>
<td>African American adolescents</td>
<td>S</td>
<td>No</td>
</tr>
<tr>
<td>Medical Trauma</td>
<td>Resilience Scale</td>
<td>Women 1 – 5 years after beratric surgery</td>
<td>S</td>
<td>No</td>
<td>Dethanomenos et al. (2013)[19]</td>
</tr>
<tr>
<td></td>
<td>Hospital Anxiety-Diabetes Scale</td>
<td>Breast cancer patients</td>
<td>NS</td>
<td>No</td>
<td>Green et al. (2009)[19]</td>
</tr>
<tr>
<td></td>
<td>Basic Depression Inventory</td>
<td>African American patients with type 1 diabetes</td>
<td>NS</td>
<td>Yes</td>
<td>Roy et al. (2010)[13]</td>
</tr>
<tr>
<td>Traumatic Brain Injury, Perceived Limitations</td>
<td>CD-RISC</td>
<td>Veterans with and without TBI</td>
<td>L</td>
<td>Yes</td>
<td>Graham et al. (2013)[19]</td>
</tr>
<tr>
<td>Mental Stress</td>
<td>CD-RISC</td>
<td>Children and adolescents with ODD and or ADHD</td>
<td>S</td>
<td>No</td>
<td>Marsh et al. (2012)[10]</td>
</tr>
<tr>
<td>Children Perception of Inter-parental Conflict</td>
<td>ODD symptoms</td>
<td>Children and adolescents with ODD and or ADHD</td>
<td>S</td>
<td>No</td>
<td>Marsh et al. (2012)[10]</td>
</tr>
<tr>
<td>Age</td>
<td>CDRISC-10</td>
<td>Community-dwelling Caucasian older adults</td>
<td>NS</td>
<td>Yes</td>
<td>C’bene et al. (2012)[10]</td>
</tr>
</tbody>
</table>

Involved Potentially Traumatic Event
- Natural Disasters
  - Hurricane Related Traumatic Experiences-Repeated Exposure
  - Perceived Racial Discrimination
- Major Stressors
  - Child maltreatment
  - Medical Stressor
  - Ambulatory care
- Subtle Stressors
  - Negative affective pictures
  - Emotional faces
  - Visual stimuli, electrical stimulation
- Negative world
  - Boredom
  - Uncontrolled, unpleasant, stressful events

Terry Social Stress Test (free speech, mental arithmetic)
- Profile of Mood States
  - Undergraduate students | S | Yes | Terri et al. (2012)[10] |
  - University students | S | Yes | Terri et al. (2012)[10] |

Discussion & Conclusion
- The hypothesis is partially supported by the analysis because the majority of the studies (17/26, 65%) found that S allele carriers are less resilient.
- Nevertheless, 4/26 (15%) of the studies found that S allele carriers are more resilient and 5/26 (20%) found no statistically significant association between 5-HTTLPR and resilience.
- 3 dimensions of the articles may explain the inconsistent results.
- 1) Definition of resilience
- No single agreed-upon definition of resilience.
- Emergent resilience represents trajectories of positive adjustment in the context of chronically stressful circumstances.
- Minimal-impact resilience is applied in the context of minimal-impact and chronic stressful circumstances.
- Future studies should more clearly conceptualize and operationalize resilience, genotype rs25531, and investigate the environment in a full range in order to address the differential susceptibility.

- 2) An A/G single nucleotide polymorphism (SNP)
  - There is a A/G SNP (rs25531) in the L allele.
  - The L allele is associated with the higher basal activity whereas the L allele has transcriptional activity no greater than the S allele.
  - Because 5-HTTLPR is a triallelic locus (La, Lg, and S) and three of them appear to act codominantly, the alleles in the triallelic genotypes may be reclassified by their level of expression as follows: L'/L' (La/La); L'/S (La/Lg, La/S), and S'/S' (Lg/Lg, Lg/S, S/S).
  - Among 26 studies reviewed in this article, only 11 (42%) studies also investigated rs25531.

- 3) Gene by environment (G x E) interaction and the differential susceptibility
  - Gene expression is responsive to the environment.
  - A G x E interaction occurs when the effect of exposure to an environment risk factor on health and behavior is moderated by variation in specific genes.
  - The differential susceptibility proposed the more susceptible individuals are disproportionately influenced by both negative and positive environments in a “for better and worse” outcome.
  - Some of the S allele carriers who are hypothetically less resilient have physiologically adjusted to the chronically stressful circumstances.

- Future studies should more clearly conceptualize and operationalize resilience, genotype rs25531, and investigate the environment in a full range in order to address the differential susceptibility.


- 5-HTTLPR maps to 17q11.1-17q12 (on the long arm of chromosome 17).
- 5-HTTLPR contains a 43 base pair insertion or deletion in the 5' regulatory region of the gene.
- The short (S) 5-HTTLPR variant (purple) produces significantly less 5-HTT mRNA and proteins than the long (L) variant (red).
- Individuals who carry the S allele of 5-HTTLPR have increased characteristics of fear conditioning, auditory startle, sympathetic reactivity, HPA axis reactivity, etc.