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

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Background
- Most people are exposed to potentially traumatic events at some point in their lives, but many are surprisingly resilient.1
- Resilience is a complex multi-dimensional construct.2
- The heritability of resilience is .38 - .52 among US adults.3
- Resilience is polygenic with at least 9 candidate genes.4
- Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR) is of increasing clinical interest.5

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 an isolated potentially traumatic event
  - 2. An A/G single nucleotide polymorphism (SNP)
     - There is a A/G SNP (rs25531) in the L allele
     - The La allele is associated with the higher basal activity whereas the Lg 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)8
  - 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 environment16
  - 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 genes17
  - The differential susceptibility proposed the more susceptible individuals are disproportionately influenced by both negative and positive environments in a "for better and worse" outcome18
  - 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 full range in order to address the differential susceptibility

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

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

Stress / Trauma Measure | Resilience Measure | Sample | Finding (Less resilient) | rs25531? | Authors (Year)
--- | --- | --- | --- | --- | ---
Childhood maltreatment | Children's Depression Inventory | Mediated & nonmediated children | L | No | Barry et al. (2013)8
Childhood Trauma Questionnaire | Youth Self-Report (depression/anxiety and somatic symptoms) | Mediated & nonmediated adolescents | S | No | Cicchetti & Rogosch (2012)10
Childhood Trauma Questionnaire | Early Adolescent Temperament Questionnaire-Revised (effortful control) | Dutch adolescents | S | No | Cicchetti et al. (2007)9
Distal (Adverse Childhood Events) and proximal (Recent Life Stressors) stressful life events | Zung Self-Rating Depression Scale (CD-RISC as "buffer") | General population | L | No | Carli et al. (2011)12
Childhood Trauma Questionnaire | CDRSSC-10 | Undergraduate students | S | Yes | Nederfert et al. (2010)10
Adolescent Trauma | CD-RISC-10 | Individuals from the Detroit Neighborhood Health Study | S | No | Nietzel et al. (2014)9
Number of traumatic events | PTSD Checklist | African exposed to trauma | Not Significant (NS) | No | Koenen et al. (2011)11
Perceived Resilience
Schedule of Racist Events (perceived racial discrimination) | Conduct problems | African American youths | S | No | Brody et al. (2011)12
Schedule of Racist Events (perceived racial discrimination) | Physical health, mental health, trouble with the law, & social relationships | African American adolescents | S | No | Gibbons et al. (2012)12
Medical Trauma
Severe obesity treated by bariatric surgery | Resilience Scale | Women 1 – 5 years after bariatric surgery | S | No | Delfourrines et al. (2012)12
Childhood Trauma Questionnaire | Hospital Anxiety Depression Scale | Breast cancer patients | S | Yes | Grewe et al. (2012)12
Children Perception of Inter-parental Conflict | Basic Depression Inventory | African American patients with type 1 diabetes | NS | Yes | Roy et al. (2010)13
Mental stress | CD-RISC | Veterans with and without TBI | L | Yes | Shain et al. (2010)14
Children Resilience | ODD symptoms | Children and adolescents with ODD and or ADHD | S | No | Martel et al. (2012)13
Aging
Self-Rated Successful Aging | CDRSSC-10 | Community-dwelling Caucasian older adults | NS | Yes | Bierla et al. (2012)12
Isolated Potentially Traumatic Event
Natural Disasters
Hurricane Related Traumatic Experiences-Related | PTSS-Reaction Index for Children-Revised | Children exposed to Hurricane Ike | NS | No | La Greca et al. (2013)12
Maltreatment
Distress intolerance | Behavioral Indicator of Resilience to Distress | Youths from Washington, D.C. | S | No | Arrasteh et al. (2012)12
A narcissistic stressor (school final examinations) | Reward responsivity | Bulgarian high school students | S | Yes | Nikolov et al. (2012)12
Emotional basis
Negative affective pictures | Based attention for emotional stimuli | General population | S | No | Fox et al. (2009)15
Emotional basis
Visual stimuli, electrical stimulation | Reactivity in the amygdala and subgenual cingulate cortex | European volunteers | S | Yes | Carter et al. (2011)8
Negative word | Based attention for emotional stimuli | Unmedicated, young adults with low current depression and anxiety symptoms | S | Yes | Kwon et al. (2010)12
Trier Social Stress Test (free speech, mental arithmetic) | Positive and Negative Affect Scale, & Negative Affective Priming | University students | S | Yes | Markus & De Raedt (2011)12
Profile of Mood States | Undergraduate students | S | Yes | Verschoor & Markus (2011)12

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