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Kosuke Niitsu

University of Nebraska Medical Center, KosukeNiitsu@gmail.com

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

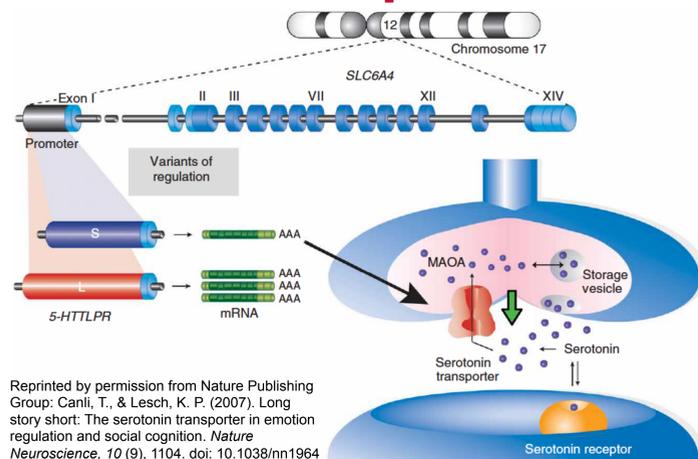
Kosuke Niitsu, MSN, APRN-NP, PMHNP-BC

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 resilient¹
- Resilience is a complex multi-dimensional construct²
- The heritability of resilience is .38 - .52 among US adults³
- Resilience is polygenic with at least 9 candidate genes⁴
- Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR) is of increasing clinical interest⁵

Serotonin Transporter Gene



- 5-HTTLPR maps to 17q11.1-17q12 (on the long arm of chromosome 17)⁶
- 5-HTTLPR contains a 43 base pair insertion or deletion in the 5' regulatory region of the gene⁷
- The short (S) 5-HTTLPR variant (purple) produces significantly less 5-HTT mRNA and proteins than the long (L) variant (red)⁸
- Individuals who carry the S allele of 5-HTTLPR have increased characteristics of fear conditioning, auditory startle, sympathetic reactivity, HPA axis reactivity, etc.⁹

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

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 circumstances¹⁰
 - Minimal-impact resilience is applied in the context an isolated potentially traumatic event¹⁰

- (2) An A/G single nucleotide polymorphism (SNP)
 - There is a A/G SNP (rs25531) in the L allele¹¹
 - The La allele is associated with the higher basal activity whereas the Lg allele has transcriptional activity no greater than the S allele^{12,13}
 - Because 5-HTTLPR is a triallelic locus (La, Lg, and S) and three of them appear to act codominantly,¹⁴ 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)¹⁵
 - 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 a full range in order to address the differential susceptibility

Stressor / Trauma Measure	Resilience Measure	Sample	Finding (Less resilient)	rs25531?	Authors (Year)
Chronically Stressful Circumstances					
<i>Childhood Maltreatment</i>					
Children's Social Experiences Questionnaire (peer victimization)	Children's Depression Inventory	Maltreated & nonmaltreated children	L	No	Banny et al. (2013) ¹⁹
Maltreatment Classification System	Resilient functioning	Maltreated & nonmaltreated children	S	No	Cicchetti & Rogosch (2012) ²⁰
Childhood maltreatment	Youth Self Report (depression/anxiety and somatic symptoms)	Maltreated & nonmaltreated adolescents	S	No	Cicchetti et al. (2007) ²¹
<i>Childhood Trauma</i>					
Childhood Trauma Questionnaire	Connor-Davidson Resilience Scale (CD-RISC)	Male prisoners	L	No	Carli et al. (2011) ²²
Childhood adversities	Early Adolescent Temperament Questionnaire-Revised (effortful control)	Dutch adolescents	S	Yes	Nederhof et al. (2010) ²³
Distal (Adverse Childhood Events) and proximal (Recent Life Stressors) stressful life events	Zung Self-Rating Depression Scale; (CD-RISC as “buffer”)	General population	S	No	Sharpley et al. (2013) ²⁴
Childhood Trauma Questionnaire	CDRISC-10	Undergraduate students	S	Yes	Stein et al. (2009) ²⁵
<i>Adulthood Trauma</i>					
Life Events Checklist	Davidson Trauma Scale (& CD-RISC)	Africans exposed to trauma	L	No	Hemmings et al. (2013) ²⁶
Number of traumatic events	PTSD Checklist	Individuals from the Detroit Neighborhood Health Study	Not Significant (NS)	No	Koenen et al. (2011) ²⁷
<i>Perceived Racism</i>					
Schedule of Racist Events (perceived racial discrimination)	Conduct problems	African American youths	S	No	Brody et al. (2011) ²⁸
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) ²⁹
<i>Medical Trauma</i>					
Severe obesity treated by bariatric surgery	Resilience Scale	Women 1 – 5 years after bariatric surgery	S	No	Defrancesco et al. (2013) ³⁰
Diagnosis of cancer within 6 months	Hospital Anxiety-Depression Scale	Breast cancer patients	NS	No	Crassi et al. (2010) ³¹
Childhood Trauma Questionnaire	Beck Depression Inventory	African American patients with type 1 diabetes	NS	Yes	Roy et al. (2010) ³²
<i>Traumatic Brain Injury, Perceived Limitations</i>					
	CD-RISC	Veterans with and without TBI	L	Yes	Graham et al. (2013) ³³
<i>Mental Illness</i>					
Children Perception of Inter-parental Conflict	ODD symptoms	Children and adolescents with ODD and/or ADHD	S	No	Martel et al. (2012) ³⁴
<i>Aging</i>					
Self-Rated Successful Aging	CDRISC-10	Community-dwelling Caucasian older adults	NS	Yes	O'Hara et al. (2012) ³⁵
Isolated Potentially Traumatic Event					
<i>Natural Disaster</i>					
Hurricane Related Traumatic Experiences-Revised	PTSD-Reaction Index for Children-Revised	Children exposed to Hurricane Ike	NS	No	La Greca et al. (2013) ³⁶
<i>Mild Stressors</i>					
Distress intolerance	Behavioral Indicator of Resiliency to Distress	Youths from Washington, D.C.	S	No	Amstadter et al. (2012) ³⁷
A naturalistic stressor (school final examinations)	Reward responsiveness	Bulgarian high school students	S	Yes	Nikolova et al. (2011) ³⁸
<i>In Vitro</i>					
Negative affective pictures	Biased attention for emotional stimuli	General population	S	No	Fox et al. (2009) ³⁹
Emotional faces	Reactivity in the amygdala and subgenual cingulate cortex	European volunteers	S	Yes	O'Nions et al. (2011) ⁴⁰
Visual stimuli, electrical stimulation	Skin conductance responses & neural responses	General population	S	Yes	Hermann et al. (2012) ⁴¹
Negative word	Biased attention for emotional stimuli	Unmedicated, young adults with low current depression and anxiety symptoms	S	Yes	Kwang et al. (2010) ⁴²
2-minute serial subtraction sessions and cold-pressure exposures	Positive and Negative Affect Scale, & Negative Affective Priming	University students	S	Yes	Markus & De Raedt (2011) ⁴³
Trier Social Stress Test (free speech, mental arithmetic)	Profile of Mood States	Undergraduate students	S	Yes	Verschoor & Markus (2011) ⁴⁴