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5HTTLPR Short Allele, Resilience and Successful Aging in Older Adults

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Abstract

Objective—Resilience is proposed as a significant component of successful aging. Young adult carriers of the Serotonin Transporter Polymorphism (5HTTLPR) short(s) allele appear to have reduced resilience to stress. We examined if presence of the short allele was associated with poorer emotional resilience in older adults.

Methods—In a cross-sectional study of 99 healthy, community-dwelling, older adults we determined 5HTTLPR genotype status and administered the Connor-Davidson Resilience Scale and self-reported measures of successful aging, cognition and health.

Results—There was no significant association between the 5HTTLPR s allele and resilience. S allele carriers had worse cognition and self-report ratings of successful aging.

Conclusions—These findings suggest that the impact of the 5HTTLPR s allele on stress-related outcomes may attenuate with older age. However, s allele status appears to be a biomarker of poorer self-rated successful aging, and cognitive performance in older adults.

Keywords

5-HTT; Serotonin transporter polymorphism; Resilience; Stress; Successful Aging; Cognition

Introduction

Stress occurs throughout the lifespan and can be viewed as a normal component of the human experience. Recently, the construct of resilience to the negative impact of stressful events has garnered significant research attention. Stein et al. (1) define resilience as the ability to maintain healthy and stable levels of psychological functioning when exposed to stressful and traumatic events. One component of this construct is emotional resilience, which has been defined as resistance to, or adaptation to, the development of psychological disorders even when stress or trauma occurs (2).

The serotonin transporter polymorphism (5HTTLPR) is one genetic risk factor implicated in the development of psychopathological response to stress (3). The short or deletion form - the s allele - is associated with reduced transcription and reuptake efficiency within the serotonergic system. Research on the s allele has focused dominantly on its role in depression, anxiety, and anxiogenic personality traits in response to environmental stress (3). In a sample of 423 undergraduates, Stein et al. (1) found s allele carriers had reduced resilience to stress, as measured by the Connor-Davidson Resilience Scale (CDRISC-10).

Most recently, investigators have begun to consider whether resilience is a component of healthy or successful aging (4). In 1,395 community-dwelling women over age 60, Lamond et al. (5) found the CD-RISC to be significantly correlated with multiple self-reported measures of successful aging (i.e. self-reported successful aging, optimism, emotional well-being, social engagement). However, our prior research indicates that the association of the 5HTTLPR s allele with psychopathological response to stress may attenuate with increased age (6, 7). It is thus unclear whether any association of the s allele with reduced resilience to stress would also be observed in older adults. We are unaware of any study that has investigated this issue. We hypothesize that the 5HTTLPR s allele would be associated with lower levels of resilience in older adults, as measured by the CDRISC-10. In secondary analyses, we examined the independent relationships among 5HTTLPR allele status, resilience and additional measures of successful aging, including self-report measures of how successfully one is aging, health, and cognition.

Materials and Methods

A total of 99 community-dwelling, Caucasian older adults, ages 55 to 100 ($M = 71.5$; $SD = 8.8$) with a mean of 16.2 years of education ($SD = 2.8$), completed the CDRISC-10, which was part of a broader Successful Aging questionnaire they completed in an ongoing investigation of stress and cognition. These subjects have been previously reported upon (6) and were recruited through advertisements and local senior centers. Participants provided informed consent in accordance with Stanford University IRB regulations. Individuals were excluded if they had a Mini-Mental Status Exam (8) score less than 26; any Axis I disorder, assessed by the Structured Clinical Interview for DSM-IV-TR (9); and using any systemic corticosteroids, psychotropic medication, short-acting anxiolytics, sedative hypnotics, or medications for the treatment of dementias.

Participants had whole blood drawn at the Stanford Clinical Research Unit, which was transported directly to the genetics laboratory for DNA extraction from 200 μ l of blood using the Qiagen DNeasy Kit (Cat.#69506). 5HTTLPR genotype status was determined using standard methods, as previously described (6). Thirty-one subjects were homozygous for the l allele and 68 subjects had at least one s allele.

Measures

Resilience

The Connor–Davidson Resilience Scale (CDRISC-10) consists of 10-items measuring resilience to stress, and has been used with both general and patient populations (10). Ratings are on a Likert-type scale and includes items such as “I am able to adapt when changes occurs,” with each item scored 0 “Not True at All” through 4 “True Nearly All of the Time.” The scale possesses good internal consistency and convergent validity in older adults (5).

Successful Aging

The Successful Aging questionnaire has been previously employed (see reference 11 for full details). Attitudes/perceptions toward aging were assessed by a single-item rating of Self-Rated Successful Aging scored from 1 (lowest) to 10 (highest), and the five item Satisfaction with Life Scale (12).

Cognition

Test-based cognitive performance was assessed with the Cognitive Assessment Screening Test (CAST), a brief measure of global cognitive status, which is a (13).

Physical and Mental Health-Related Quality of Life

Physical and Mental Health-Related Quality of Life was assessed with the MOS-RAND SF-36 physical and mental health component subscales (14).

Analyses

We examined the data for outliers, missing values, and computed summary statistics for demographics. Differences in demographics were compared across subgroups defined by 5HTTLPR status, using Fisher exact tests for discrete and t-tests for continuous variables, with the unequal variance assumption and degrees of freedom computed using the Satterthwaite approximation. For non-normally distributed continuous variables Mann-Whitney U tests were used instead. Primary analyses focused on the relationship between the 5HTTLPR short allele (0=no short allele and 1=at least one short allele) and the CDRISC-10 measure of resilience.

Secondary analyses were conducted to investigate the association between other successful aging related variables (CAST, Self-Rated Successful Aging, Satisfaction with Life Scale, and MOS-RAND SF-36 physical and mental health subscales) and 5HTTLPR status.

We next performed t-tests or Mann-Whitney U tests to examine the relationships of resilience and other successful aging-related outcomes and 5HTTLPR status. In post-hoc analyses we examined the interaction of age and 5HTTLPR status on the CDRISC-10 measure of resilience by dichotomizing age using a median split (median age=70) and performing a t-test for 5HTTLPR status on each age group separately.

Results

Means (with SD) and frequencies of demographic and successful aging variables are presented in Table 1. None of the demographic variables differed significantly by 5HTTLPR allele status. CDRISC-10 did not differ significantly across 5HTTLPR groups. In secondary analyses Self-Rated Successful Aging and CAST scores were both significantly worse in the 5HTTLPR group with at least one short allele. There were no significant differences by 5HTTLPR group on the SWLS or MOS SF-36. For full results see Table below.

Post-hoc analyses found that in subjects below 70 years of age CDRISC-10 scores were significantly higher for subjects with no s allele (i.e. homozygous for the long or 'l' allele) ($t=2.23$, $df=45$, $p=0.030$) but there was no difference by allele status for subjects over the age of 70 ($t=-0.61$, $df=23$, $p=0.549$). A regression of CDRISC-10 on age (treated as a continuous variable) and allele status controlling for gender, education, income, and marital status also found a significant interaction (coef=0.51, se=0.26, $p=0.050$).

In 2006, Hu et al. (15) reported a single nucleotide polymorphism which gives rise to two functional variants of the L allele. The Lg variant occurs in approximately 6.5% of

Caucasian Americans and has been suggested to be associated with comparable levels of serotonin transporter expression levels to the s allele. We also genotyped our sample for this variant but only 4 of our ll homozygote sample had the La/Lg genotype. We reran all analyses with these four individuals included with the s allele carrier group and there was no difference to our results.

Discussion

Contrary to our primary hypothesis, the 5HTTLPR s allele was not associated with lower resilience in older adults. Our primary finding stands in contrast to that of the Stein et al. study (1), who observed a significant association between reduced levels of resilience and the s allele in younger adults. This may reflect that our older participants were healthy and had a relatively high socioeconomic status, so they may not have been exposed to levels of stress sufficient to register resilience on the CDRISC-10, compared to the participants in the Stein et al. study (1), who, as undergraduates, may experience more day-to-day stress. Alternatively, it may reflect the larger sample of 423 undergraduates in their investigation, which likely resulted in greater power to detect the association. One limitation of our study when compared to the Stein et al (1) investigation is that we did not have sufficient numbers of individuals to examine the s allele homozygotes as a separate group. Indeed, it should be noted that the mean difference on the CDRISC-10 between l allele homozygotes and s allele carriers was very similar in our and the Stein et al. investigation (1). Further, there are other aspects of stress resilience, such as social support, that were not considered in our investigation, and which may act as additional modifiers of any relationship of 5HTTLPR and resilience. As such, our lack of an association cannot be taken as evidence of the null hypothesis.

While reduced power may account for our findings, a substantial literature suggests that as individuals age they process more positive information and ignore more negatively valenced content (16). Thus, another explanation for our findings is that increased resilience in older adults offsets any negative impact of the s allele on resilience. Age-related increases in resilience may account for the apparent attenuation of the negative interactive relationship of stress and the s allele on psychiatric symptoms in older adults (6, 7), although it must be noted that not all studies observe increased resilience with age (5).

Given the broad age range of our sample, we conducted post-hoc analyses which found no age-related difference among s allele carriers on their CDRISC-10 scores. However, individuals homozygous for the l allele who were younger than 70 years of age had higher levels of resilience, an effect that disappeared over age 70. Thus, rather than increased resilience with age accounting for the lack of association of the s allele with lower resilience in older adults, it may be that age-related depletions in serotonergic neurotransmitter efficiency (17) reduce any difference between the impact of the l and the s alleles (7). Longitudinal investigations are required to address whether there are age-associated within-person changes in the impact of 5HTTLPR on stress-related outcomes, and whether such changes reflect a diminishment of any protective effect of the l allele, or an exacerbation of the negative effects of the s allele.

In contrast to the observed lack of association of 5HTTLPR with resilience, s allele carriers had lower cognitive abilities as measured by the CAST, as well as lower self-rated successful aging (SRSA). We have previously observed the s allele to be associated with poorer cognitive functioning in older adults (6). Several recent studies have implicated the 5HTTLPR s allele in poorer cognitive functioning (18, 19). This raises the question of whether the frequently observed interactive effect of stress and 5HTTLPR s allele on increased risk for worse mood is mediated by impairments in dealing with stress that reflect

more fundamental deficits in cognitive functioning. If this were the case, given that our older participants were healthy with relatively high socioeconomic status, it might account for the negative association of poorer cognition with s allele status, but lack association with resilience since they may not have been exposed to sufficient levels of stress to invoke a resilience response. Our findings also suggest that cognitive function rather than emotional resilience may be more important to s allele carriers' sense of successful aging.

The limitations of the current study include its cross-sectional design, lack of more in-depth measures of stress and resilience, and insufficient power to consider the 5HTTLPR genotype groups and a/g variants separately. Future research, particularly longitudinal studies, are needed to more fully understand and delineate the relationship between the emotional and cognitive components of successful aging, and how these may be impacted by genetic moderators such as 5HTTLPR status.

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TABLE 1
Demographics, Resilience, and Successful Aging-Related Outcomes by 5HTTLPR Status

	5HTTLPR=0 (31)	5HTTLPR=1(68)	Test (df)^I	p-value
<u>Demographics</u>				
Age	71.2 (7.7)	72.0 (8.2)	-0.48(61)	0.632
Female	16 (51.6%)	36 (52.9%)	- *	1.000
Education (Years)	16.06 (2.66)	16.46 (2.43)	-0.70(54)	0.489
Income:				
<=\$25,000	5 (18.5%)	12 (19.7%)	- *	0.356
\$25,001-\$45,000	6 (22.2%)	16 (26.2%)		
\$45,001-\$65,000	3 (11.1%)	12 (19.7%)		
\$65,001-\$100,000	10 (37.0%)	12 (19.7%)		
\$100,001-\$150,000		3 (11.1%)	4 (6.6%)	
\$150,000-\$200,000		0 (0.0%)	5 (8.2%)	
Married	12 (61.3%)	38 (56.7%)	- *	0.826
<u>Resilience and other Successful Aging-Related Measures</u>				
CDRISC-10	70.08 (10.01)	67.35 (11.21)	0.98(63)	0.331
SRSA	8.42 (1.29)	7.88 (1.40)	1309**	0.044
SWLS	25.52 (5.48)	23.46 (6.00)	1.67(64)	0.099
CAST	19.67 (1.47)	18.97 (1.54)	1117**	0.025
MOS SF-36 Mental component	55.10 (8.26)	52.69 (8.41)	1287**	0.079
MOS SF-36 Physical component	43.48 (10.13)	42.94 (10.04)	1112**	0.667

Note:

^I Degrees of freedom for t-test computed assuming unequal variances and using the Satterthwaite approximation

* Fisher exact test

** Mann-Whitney U test

5HTTLPR = Serotonin Transporter Polymorphism

CDRISC-10= Connor-Davidson Resilience Scale¹

SRSA=Self-Rated Successful Aging

SWLS= Satisfaction with Life Scale

CAST= Cognitive Assessment Screening Test

MOS SF-36= Medical Outcomes Study-Short Form 36 Items