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Gender specific gene–environment interactions on laboratory-assessed aggression

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Abstract

We examined gene–environment interactive effects on aggressive behavior among men and women genotyped (short versus long alleles) for the serotonin transporter gene. Aggressive behavior was indexed via a laboratory paradigm that measured the intensity and duration of shocks delivered to a putative ''employee''. Half of the participants were exposed to a physical stressor during the procedure (stress) and half were not (no-stress). Participants' physiological responses were gauged via acoustic startle eyeblink reactions (startle reactivity). Results were that men with the homozygous short (s/s) genotype showed increased aggression only under stress, whereas women and men carrying the long allele did not show differences in aggression in stress versus no-stress. However, although stress exposure produced increases in startle reactivity, there were no genotype or gender differences in physiology. These results replicate longitudinal research findings confirming the interactive effects of genes and environment on behavioral reactivity and on the development of externalizing psychopathological syndromes, at least in men.

Keywords: Aggression; Serotonin transporter gene; Gender; Stress; Genetics; Startle

Cases of violence have a dramatic impact on societal well-being, policy-making, and child-rearing practices. For this reason, understanding the combined biological and environmental risk for engaging in destructive behaviors has become the main focus of study for many social scientists. Diathesis-stress explanations of aggression suggest that research should be conducted to identify potential intrapersonal factors, including genetic susceptibility, as well as environmental stress that may interact to increase risk for aggression.

Prior empirical work has attempted to verify the interactive effects of individual differences and environmental stress on aggression, but these studies have focused on personality traits and not genes in particular. For example, Little and Garber (2004) reported that academic stressors and transition to high school prospectively predicted aggressive symptoms only among adolescents who exhibited personality traits associated with reactivity to failure. In the laboratory, Netter et al. (1998) reported that individuals scoring high on personality traits related to neuroticism exhibited significantly higher aggression responses primarily following interpersonal provocation. In a more recent study, Verona et al. (2002) exposed a subgroup of male participants to an on-going physical stressor (intermittent air blasts) within a laboratory aggression paradigm. Analyses revealed that participants who were high on trait negative emotionality exhibited increases in tonic physiological responses and a corresponding tendency toward greater aggression only after exposure to the persistent stressor. This was a demonstration that personality traits can predispose to aggressive behaviors under general stress conditions, and not just interpersonal provocation.

Considering these data, a direct examination of genetic predispositions can lead to better identification of persons at risk to respond to stress with aggression. The present laboratory study represents an examination of genetic (serotonin transporter gene) and acute environmental (stress) influences on aggressive behavior and physiological reactivity in normal men and women.

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1. Serotonin transporter gene

With the recent interest in human DNA sequencing and discoveries of several gene loci implicated in disease risk, psychopathologists have begun to study the influence of identified genes on the development of mental disorders. The serotonin transporter gene (5HTT), which is involved in the regulation of serotonin neurotransmitter (5HT) reuptake and the availability of 5HT in the synaptic cleft, has been one of the most widely investigated genes in relation to psychiatric disorders and syndromes (Brown and Joiner, 2004). In humans, 5HTT is encoded on one gene (SLC6A4), located on chromosome 17q12. The transcriptional control region of this gene, denoted 5HTTLPR, has been identified as having a polymorphism consisting of a 44 base pair insertion or deletion. These two alleles have been called the long (L) and short (S), respectively (see Lesch et al., 1996). The alleles combine in individuals to form three different genotypes—the homozygous short (s/s), homozygous long (l/l) and heterozygous (s/l) genotypes. Cells with the L allele produce higher concentrations of 5HTT mRNA than cells with the S allele, which leads to increased production of 5HTT and thus more rapid clearance of 5HT from the synaptic cleft among those carrying the L allele. In essence, individuals with the S allele will most likely have decreased 5HT reuptake, and in fact, this reduced reuptake has been confirmed in human blood platelets (Greenberg et al., 1999).

Lesch (2001) suggested that it may be the case that impairment in the clearance of 5HT in the synaptic cleft and the subsequent increases of the neurotransmitter near serotonergic cells and dendrites may activate a receptor-mediated negative feedback that leads to an overall decrease of 5HT neurotransmission. This hypothesis is preliminary; nonetheless, Hanna et al. (1998) did report that humans with the s/s genotype had significantly lower levels of blood 5HT than did those carrying the l/s or l/l genotype. Additionally, Higley et al. (1998) reported an interesting demonstration of gene–environment interactions on biological systems in nonhuman primates. They found that rhesus monkeys carrying the low-functioning 5HTT S allele, who were also deprived of maternal care early in life, had significantly lower concentrations of a 5HT metabolite (5HIAA) in the cerebral spinal fluid (CSF). Genotype did not relate to 5HIAA functioning among normal mother-reared monkeys. This confirms the idea that the examination of the moderating influence of environment on gene–affect and gene–behavior relationships is necessary to clarify mixed findings.

2. Serotonin transporter predisposes to aggression and physiological reactivity

In the area of aggression and impulsive behaviors, scientists have reported reliable relationships between dysregulated serotonin (5HT) neurotransmitter functioning and self-reported or naturalistic aggression in humans and non-human mammals. These data are extensive and have been reviewed elsewhere (Roy et al., 1990; Verona and Patrick, 2000). Relationships between 5HT functioning and aggression have also been shown in the laboratory (Moeller et al., 1998). Very few studies have examined 5HTT genotype links to externalizing behaviors and impulsivity, particularly aggression and violent suicide, with inconsistent results. Lesch (Lesch and Merschdorf, 2000; Lesch, 2001) and others (Zalsman et al., 2001) have found that humans and non-human primates with histories of violent behavior and aggressive traits are more likely to carry the 5HTT S allele, as are persons engaging in suicide attempts (Preuss et al., 2001; Bondy et al., 2000) and those with family histories for suicide (Joiner et al., 2002). However, these relationships have not been found consistently (Rujescu et al., 2001, in the case of suicide; Patkar et al., 2002, in the case of aggressive traits). The case can be made that inconsistent findings reflect the absence of gene main effects and implicate the need to investigate gene-by-environment effects on aggressive behavior.

In addition to 5HTT links to aggression, the 5HTT S allele may generally predispose to increased physiological reactivity in response to environmental stressors. In a neuroimaging study, Hariri et al. (2002) reported that human carriers of the S allele showed higher amygdala activation in response to fearful stimuli. McCaffery et al. (2003) found that persons homozygous for the short allele exhibited increased heart rate responses to a psychological challenge, although this was more the case for women than men. Barr et al. (2004) found that a similar polymorphism (low transcriptional efficiency) in the promoter region of the 5HT-transporter of a non-human animal (rhesus monkey) was associated with an altered adrenocorticotropic hormone response to separation from mother. Thus, the hypothesis that the 5HTT short allele may represent a risk factor for higher levels of physiological reactivity has been supported in preliminary research with human and non-human animals. The present study involved an investigation of whether 5HTT is linked to increased behavioral (aggression) and physiological (startle) responses to stress in the laboratory.

3. Gender differences in neurobiological correlates of aggression

Gender differences in risk factors for aggression also warrant systematic attention. Perpetrators of aggressive and antisocial acts are more likely to be men, although these differences can be reduced to some extent under provocation (Bettencourt and Miller, 1996). Importantly, preliminary work indicates differential correlates/precipitants of aggression in men and women. For example, research has indicated that men and women respond differently to stress, with men showing more aggressive responses and women showing