Running Head: EMOTION REGULATION BUFFERS G X E RISK

Emotion Regulation Protects Children from Risk Associated with the 5-HTT Gene and Stress

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Abstract

Carrying a short allele in the serotonin transporter polymorphism (5-HTTLPR) while experiencing stressful environments is linked to risk for depression. Genes and environment are not easily changed, which raises the question of what factors may protect individuals from this risk. We hypothesized that individuals' ability to decrease their stress responses via effective emotion regulation may be an important protective factor and examined this hypothesis in a socioeconomically-diverse sample of 205 children aged 9-15 years. At-risk children (short-allele carriers in high-stress contexts) exhibited more depressive symptoms than other groups. Importantly, at-risk children who used effective emotion regulation were protected from increased depressive symptoms. These results have important implications for the basic science of understanding risk and resilience: in addition to genes and environment, individuals' agentic ability to self-regulate may need to be considered as a critical third factor. Given that emotion regulation is learnable, these results also have strong public-health implications.

Emotion Regulation Protects Children from Risk Associated with the 5-HTT Gene and Stress

Research supports a robust link between stress and depression (Hammen, 2005). This link is pernicious not only because depression remains one of the primary causes of disability and disease burden in the world (Murray & Lopez, 1997), but also because life stress is exceptionally common (Lazarus, 1993). The link between high stress and depression appears to be further exacerbated in people who carry a short allele in the serotonin transporter polymorphism (5-HTTLPR, linked to serotonin function) (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Caspi et al., 2003; Kim et al., 2007; Lesch et al., 1996), a group that represents approximately 40-70% of the general population (Kim et al., 2007). This group appears to be particularly sensitive to the quality of their environment (Belsky & Pluess, 2009; Hankin et al., 2011; Taylor et al., 2006). Given that we cannot very easily change our genes or our stressful environments, how can people with this risky combination avoid depression? The present research examined this question by assessing the hypothesis that an individual's agentic, self-regulatory behavior can protect against gene-by-environment risk.

The mechanisms by which gene-by-environment risk leads to depression may point to specific ways to counteract the risk. One such mechanism strongly suggested by a substantial body of research is emotional reactivity (Caspi et al., 2010). Specifically, short-allele carriers compared to non-short-allele carriers demonstrate increased negative emotional reactivity to stressors (e.g., threatening images) (Gunthert et al., 2007; Hariri et al., 2002; McCaffery, Bleil, Pogue-Geile, Ferrell, & Manuck, 2003). Elevated negative emotional reactivity to stress, in turn, has been linked with depression (Cohen, Gunthert, Butler, O'Neill, & Tolpin, 2005). Given these

links, several models hold that negative emotional reactivity is a mechanism linking gene-by-environment risk and depression (e.g., Caspi et al., 2010).

It follows that individuals' ability to reduce their own negative emotional reactivity, or *emotion regulation* (Gross, 1998), may offset the risk imposed by a short allele in stressful environments. One strategy shown to be particularly effective for reducing negative emotions is cognitive reappraisal (Gross & John, 2003; McRae, Ciesielski, & Gross, 2012; Ochsner, Bunge, Gross, & Gabrieli, 2002; Troy, Wilhelm, Shallcross, & Mauss, 2010), a strategy that involves reframing the meaning of an event (Gross, 1998). Thus, for people whose genes and environment put them at risk (i.e., stressed individuals who carry a short allele in the 5-HTTLPR genotype), cognitive reappraisal may be a useful strategy that helps to offset this risk.

The present study examined whether the use of cognitive reappraisal attenuates the risk for increased depressive symptoms observed in highly stressed individuals with a 5-HTTLPR short allele. We examined this question in a sample of children aged 9-15, an age range when depression first develops (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). We used well-validated, standardized, and widely-used self-report measures to assess use of cognitive reappraisal (Gross & John, 2003), severity of stress experienced over the last 3 months (Hankin & Abramson, 2002), and current severity of depressive symptoms (Kovacs, 1981) in a socioeconomically-diverse sample of children. Participants were genotyped using standard protocols (Anchordoquy, McGeary, Liu, Krauter, & Smolen, 2003) to ascertain who were short-allele carriers (those with either one or two short alleles of 5-HTTLPR) and who were non-carriers (those with two long alleles of 5-HTTLPR). This grouping is consistent with prior research (Lenze et al., 2005; Otte, McCaffery, Ali, & Whooley, 2007; Ramasubbu, Tobia, Buchan, & Bech-Hansen, 2006) and with theoretical support for the dominant genetic effect of

the short allele on outcomes (Greenberg et al., 1999; Lesch et al., 1996), whether there are one or two short alleles. We predicted a three-way interaction in which short-allele carriers would experience more depressive symptoms under stress compared to their non-carrier counterparts, but that stressed short-allele carriers should experience fewer depressive symptoms if they also use cognitive reappraisal more (vs. less) often.

Methods

Participants

A sample of 205 children aged 9-15 (M = 12.01; 62% female) from the Denver, CO area was recruited as part of a larger study. The sample was largely ethnically homogeneous (75% Caucasian; 7% African American/Black; 4% Latino/Hispanic; 4% Asian/Island Pacific; 10% other/multiracial) and was socioeconomically heterogeneous with regard to yearly family income (7% <$20,000; 10% $20,001-40,000; 13% $40,001-60,000; 20% $60,001-80,000; 20% $80,001-100,000; 30% >$100,000).

Materials

Cognitive reappraisal. Children's use of cognitive reappraisal was assessed using an adapted version of the Emotion Regulation Questionnaire with simpler language more appropriate for children (Gross & John, 2003). This scale includes 6 items rated on a scale of 1 (*strongly disagree*) to 7 (*strongly agree*) measuring the extent to which the participant engages in cognitive reappraisal (e.g., I control my feelings by *changing the way I think* about the situation I'm in), α = .82.

Stress. Children's stress levels were assessed using the Adolescent Life Events Questionnaire (Hankin & Abramson, 2002), which lists 37 stressful life events. Children

indicated how often each event occurred in the past 3 months on a scale of 1 (*never*) to 5 (*always*), and responses were summed to create a composite stress severity score.

Depressive symptoms. Children's depressive symptoms were assessed using the Children's Depression Inventory (Kovacs, 1981), which contains 27 items rated on a scale of 0 (e.g., *I am sad once in awhile*) to 2 (e.g., *I am sad all of the time*) assessing the severity of psychological, social and somatic symptoms of depression. Responses were summed to create a composite score, $\alpha = .82$.

Genotyping. Children provided saliva cells for DNA collection via Oragene™ kits from DNA Genotek (Ottawa, Ontario, Canada) and genomic DNA was collected and isolated using standard salting out and solvent precipitation methods. The *5-HTTLPR* alleles were assayed (Anchordoquy et al., 2003) and modified by using primers reported by (Hu et al., 2005). Samples were analyzed on an ABI PRISM® 3130xl Sequencer. Trichotomous groups of SS (n = 38), SL (n = 99), and LL (n = 68) genotypes were formed. These genotypes were distributed according to Hardy-Weinberg equilibrium. We conducted our analyses examining the 5-HTTPLR genotype and not the functional variants of the long allele, rs25531 (i.e., L_A and L_G), because the majority of studies focused on 5-HTTLPR (Caspi et al., 2010).

Control variables. Several potential confounds were assessed and controlled for. Specifically, parents' use of cognitive reappraisal was assessed using the Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003). This scale includes 6 items rated on a scale of 1 (*strongly disagree*) to 7 (*strongly agree*) targeting the extent to which the parent engages in cognitive reappraisal, $\alpha = .84$. Parents' stress levels were assessed using the Life Events Inventory (Cochrane & Robertson, 1973), which lists 36 stressful life events. Parents indicated whether each event occurred or not in the past 3 months, and the number of affirmative

responses were summed to create a composite score. Finally, parents' depressive symptoms were assessed using the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996), which contains 21 items rated on a scale of 0 to 3 assessing the severity of psychological, social and somatic symptoms of depression. Responses were summed to create a composite score, $\alpha = .93$.

Procedure

Participants were recruited by brief information letters sent home directly by the participating school districts to families with a child in 3rd, 6th, or 9th grades of public schools in the Denver, CO area (approximately 2,000 families). The short letter stated that the experimenters were conducting a study on social and emotional development and requested that interested participants call the laboratory to receive more detailed information on the study. Three hundred and five families called the laboratory for more information. During this phone call, parents responded to a brief set of questions establishing that both the parent and child were fluent in English, that the child did not carry an autism spectrum or psychotic disorder, and that the child had an IQ > 70. Of the 305 families, 220 met these criteria and enrolled in the study. Of these 220 families, 205 (93%) completed all assessments relevant to this examination.

The parent and child visited the laboratory for the first assessment. The parent provided informed written consent for their participation and for their child; youth provided written assent. At the first assessment, children gave a DNA sample via saliva and their parents reported on the child's demographic information (sex, age, race) as well as their own socioeconomic status (as indicated by their household income). Eighteen months later, children and their parent completed a series of questionnaires assessing reappraisal, stress, and depressive symptoms. The Institutional Review Board approved all procedures. Parents and children were reimbursed for participation at each time point.

Results

We first verified that the three predictors (genotype, stress, and reappraisal) were statistically independent of each other, as evidenced by non-significant zero-order correlations between genotype and stress (r = .11, p = .11), genotype and reappraisal (r = -.06, p = .42), and stress and reappraisal (r = -.13, p = .06).

To test the hypothesis that reappraisal moderates the interactive effect of genotype and stress on depression, we entered the three-way interaction between genotype, stress, and reappraisal, all main effects, and two-way interactions in a regression analysis as predictors of depressive symptoms (all continuous variables were mean-centered and genotype was effect coded as short-allele carrier = .5, non-carrier = -.5). There was a significant main effect of stress, β = .38, $t(197) = 6.22$, $p < .001$, such that participants with higher (vs. lower) stress reported more depressive symptoms, and a significant main effect of reappraisal, β = -.27, $t(197) = 4.77$, $p < .001$, such that participants higher (vs. lower) in reappraisal reported fewer depressive symptoms. Furthermore, the previously found two-way interaction between genotype and stress was replicated, β = .21, $t(197) = 3.44$, p = .001, such that greater stress was associated with more depressive symptoms in short-allele carriers, β = .64, $t(149) = 10.09$, $p < .001$, compared to non-carriers, β = .25, $t(77) = 2.24$, p = .028.

As displayed in Figure 1, reappraisal moderated the interaction between genotype and stress, β = -.20, $t(197) = 3.68$, $p < .001$. Specifically, simple-slopes analyses (Aiken & West, 1991) revealed that highly stressed short-allele carriers reported significantly fewer depressive symptoms when they were high on reappraisal, compared to when they were low on reappraisal, β = -.43, $t(132) = 3.94$, $p < .001$. Indeed, short-allele carriers high on reappraisal reported the same number of depressive symptoms as non-carriers, whether the high-reappraisal short-allele

carriers were experiencing high levels of stress, $\beta = .07$, $t(197) < 1$, $p = .52$, or low levels of stress, $\beta = .05$, $t(197) < 1$, $p = .61$ (see Table 1 for complete results of simple effects analyses). Thus, using reappraisal completely buffered the risk associated with carrying a short allele in the context of elevated stress.

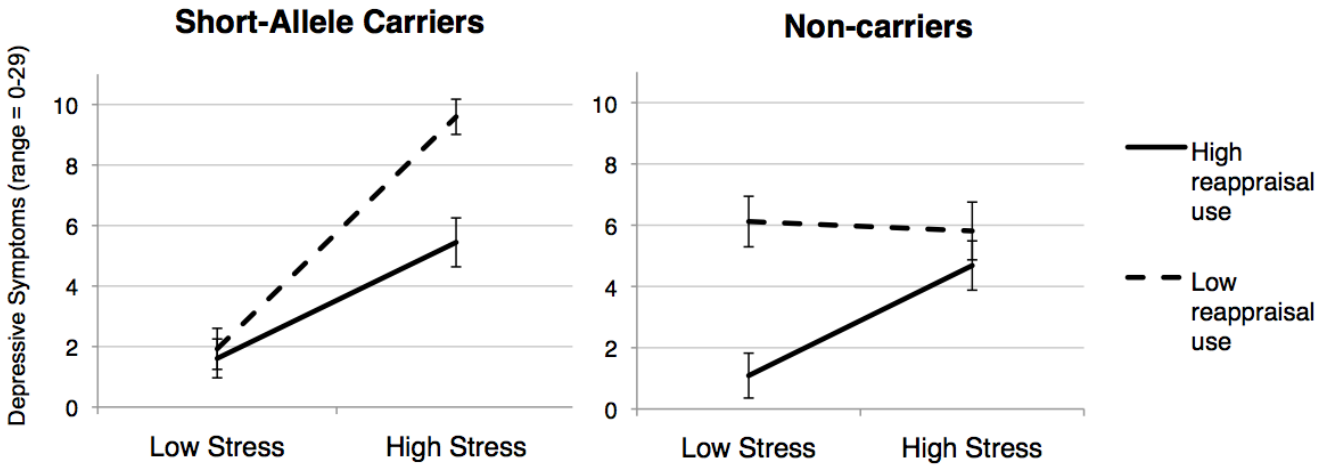

Fig. 1. Cognitive reappraisal buffers gene-by-environment risk. The figure depicts the three-way interaction between 5-HTTLPR genotype (short-allele carriers vs. non-carriers), low vs. high environmental stress (-/+ 1SD from the mean), and low vs. high use of cognitive reappraisal (-/+ 1SD from the mean) in predicting depressive symptoms. Error bars represent one standard error of the mean.

It is possible that these findings are due not to reappraisal but other factors potentially confounded with reappraisal (e.g., age, socioeconomic status). These alternative explanations, can be ruled out, because the three-way interaction remained significant when controlling for the child's age, sex, and race (Caucasian vs. other), and when controlling for the child's parents' socioeconomic status, use of cognitive reappraisal, stress level, and depressive symptoms by

including these variables simultaneously as covariates in the primary regression analysis, β = -.21, $t(76) = 2.28$, $p = .026$.

Discussion

As predicted, the present investigation supports that the mental-health risk associated with being a highly stressed short-allele carrier can be attenuated by using adaptive emotion regulation, namely cognitive reappraisal. The fact that these results were obtained in a sample of children renders the present results relevant to risk *per se*, because depression experienced in adolescence substantially increases risk for depression in adulthood (Rutter, Moffitt, & Caspi, 2006). Finally, the socioeconomically diverse sample enhances the generalizability of the findings.

Establishing cognitive reappraisal as a moderator of gene-by-environment risk has important theoretical and practical implications. Theoretically, the present results provide evidence that individuals are not necessarily at increased risk for experiencing depression in the context of a stressful environment and a 5-HTTLPR short allele. Rather, risk conveyed by this gene-by-environment interaction can be offset by a factor that is under the control of the individual. Specifically, the use of cognitive reappraisal appears to protect against the development of depressive symptoms in children who carry genetic and environmental risk to develop depression. Cognitive reappraisal may be uniquely situated to counteract the 5-HTTLPR-by-stress interaction because it allows individuals to effectively decrease negative emotional responses to stressors. More broadly, the present findings suggest that to fully understand risk and resilience, in addition to genes and environment, a third type of factor needs to be considered: individuals' agentic, self-regulatory behavior can profoundly alter the effects of gene-by-environment interactions on health.

The present findings may help resolve inconsistent results regarding the interaction between 5-HTTLPR and stress in predicting depression. Some (Karg, Burmeister, Shedden, & Sen, 2011) but not all (Risch et al., 2009) meta-analyses demonstrate this interaction. These inconsistent findings point to the presence of potential moderators of the effects of genes and environment on depression. Cognitive reappraisal appears to be one important moderator. Taking into consideration such individual-level moderators may clarify the link between gene-by-environment interactions and psychological health.

The present results also provide support for models of gene-by-environment interactions that emphasize the risk but also the potential rewards associated with the short allele (Belsky & Pluess, 2009; Boyce & Ellis, 2005; Hankin et al., 2011; Taylor et al., 2006). The differential susceptibility model proposes that certain individuals (e.g., those with a short allele) are more sensitive to their environment 'for better or worse', such that they experience worse psychological health outcomes in negative environments, yet better psychological health outcomes in positive environments, compared to their less sensitive counterparts (e.g., those without a short allele) (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007). As can be seen in Figure 1, individuals who use reappraisal less frequently exhibit this exact pattern: short allele carriers experience more depressive symptoms than noncarriers in relatively negative environments (i.e., higher stress), but experience fewer depressive symptoms than noncarriers in relatively positive environments (i.e., lower stress). Interestingly, this pattern is not present for individuals who use reappraisal more frequently. Rather, these individuals – whether they carry a short allele or not – appear not to be sensitive to their negative environments, but still experience relatively few depressive symptoms in positive environments. Using reappraisal relatively frequently, therefore, appears to promote an individual's ability to reap the benefits of positive

environments, yet not suffer from negative environments – regardless of their genetic composition.

Practically, the present results suggest a promising and cost-effective avenue for intervention and prevention, because individuals' agentic self-regulatory behavior is likely to be more amenable to deliberate change than genes or a stressful environment. Prior research confirms that young children's sense of agency can be increased with interventions (Blackwell, Trzesniewski, & Dweck, 2007). Cognitive reappraisal, specifically, is a learnable skill, as evidenced by experimental interventions among adults (Gross & John, 2003) and children as young as 10 years (McRae, Gross, et al., 2012). The fact that the present results were obtained in children further enhances their implications for prevention for two reasons. First, because children who are better at regulating themselves are more likely to become more socially, emotionally, and scholastically successful as they grow older (Mischel, Shoda, & Rodriguez, 1989), promoting self-regulation in children who are at increased genetic or environmental risk may be particularly useful. Second, because most individuals with depression experience their first depressive episode in adolescence (Costello et al., 2003) and adolescent-onset depression substantially increases risk for depression in adulthood (Rutter et al., 2006), avoiding the first episode of depression could have considerable cumulative benefits.

Overall, the present findings suggest that gene-by-environment interactions can be modulated by specific individual-level factors. These findings were also able to rule out several alternative hypotheses by accounting for important potential confounds (e.g., age, sex, and socioeconomic status). These cross-sectional results are an important first step toward a causal model in which cognitive reappraisal protects individuals from the risk that unfolds overtime as genes interact with the environment. However, it could be argued that depressive symptoms,

stress, or genes influence cognitive reappraisal, rather than the other way around. We believe this hypothesis is unlikely for both theoretical and empirical reasons. Theoretically, although cognitive reappraisal can be improved through training, it is not conceptualized as a characteristic that changes simply as a function of an individual's present symptoms or stress levels. Empirically, the three-way interaction among depressive symptoms, stress, or genes, or any of the two-way interactions therein, did not predict cognitive reappraisal, suggesting that reappraisal is not simply a side effect of these other constructs. Thus, it appears most parsimonious to conclude that reappraisal interacts with stress and genes to influence depressive symptoms. Future research would nonetheless benefit from assessing these relationships longitudinally, thus verifying the long-term implications of reappraisal in buffering gene-by-environment risk. As such, the present results highlight the important protective role that emotion regulation can have in avoiding serious psychopathology (Kovacs, Joormann, & Gotlib, 2008).

Author Contributions

B.Q.F. analyzed data and wrote the paper. A.S.T. and I.B.M. wrote the paper. A.S. performed research. B.H. designed research, performed research, and wrote the paper.

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Table 1. Summary of the simple-effect analyses decomposing the significant three-way interaction among genotype, stress, and reappraisal in predicting depressive symptoms. High and low values of stress and reappraisal were determined using values +/- 1 SD from the mean.

Stress level	Reappraisal level	Simple effect result	*β*	*t*-statistic	*df*	*p*-value
Comparing short allele carriers to non-carriers						
High	High	Short-allele carriers did not differ from non-carriers	.07	< 1	197	.52
High	Low	Short-allele carriers reported more depressive symptoms than non-carriers	.36	3.21	197	.002
Low	High	Short-allele carriers did not differ from non-carriers	.05	< 1	197	.61
Low	Low	Short-allele carriers reported fewer depressive symptoms than non-carriers	-.40	3.75	197	<.001
Comparing stress levels or reappraisal levels within short-allele carriers						
High		Reported fewer depressive symptoms when they were high (vs. low) in reappraisal	-.43	3.94	132	<.001
Low		Reported the same number of depressive symptoms whether they were high or low in reappraisal	-.03	< 1	132	.73
	High	Reported increased depressive symptoms when they were high (vs. low) in stress	.40	3.14	132	.002
	Low	Reported increased depressive symptoms when they were high (vs. low) in stress	.80	7.64	132	<.001
Comparing stress levels or reappraisal levels within non-carriers						
High		Reported the same number of depressive symptoms whether they were high or low in reappraisal	-.12	1.02	63	.31
Low		Reported fewer depressive symptoms when they were high (vs. low) in reappraisal	-.52	4.64	63	<.001
	High	Reported increased depressive symptoms when they were high (vs. low) in stress	-.01	< 1	63	.81
	Low	Reported the same number of depressive symptoms whether they were high or low in stress	.37	3.38	63	.001