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Allelic Variation of Risk for Anxiety Symptoms Moderates the Relation Between Adolescent Safety Behaviors and Social Anxiety Symptoms

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Abstract

Social anxiety often develops in adolescence, and precedes the onset of depression and substance use disorders. The link between social anxiety and use of behaviors to minimize distress in social situations (i.e., *safety behaviors*) is strong and for some patients, this link poses difficulty for engaging in, and benefiting from, exposure-based treatment. Yet, little is known about whether individual differences may moderate links between social anxiety and safety behaviors, namely variations in genetic alleles germane to anxiety. We examined the relation between adolescent social anxiety and expressions of safety behaviors, and whether allelic variation for anxiety moderates this relation. Adolescents (n=75; ages 14–17) were recruited from two larger studies investigating measurement of family relationships or adolescent social anxiety. Adolescents completed self-report measures about social anxiety symptoms and use of safety behaviors. They also provided saliva samples to assess allelic variations for anxiety from two genetic polymorphisms (BDNF rs6265; TAQ1A rs1800497). Controlling for adolescent age and gender, we observed a significant interaction between social anxiety symptoms and allelic variation (β=0.37, t=2.41, p=.02). Specifically, adolescents carrying allelic variations for anxiety evidenced a statistically significant and relatively strong positive relation between social anxiety symptoms and safety behaviors (β=0.73), whereas adolescents not carrying allelic variation evidenced a statistically non-significant and relatively weak relation (β=0.22). These findings have important implications for treating adolescent social anxiety, in that we identified an individual difference

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Conflict of Interest Sarah A. Thomas, Justin W. Weeks, Lea R. Dougherty, Melanie F. Lipton, Samantha E. Daruwala, Kathryn Kline, and Andres De Los Reyes report no conflicts of interest.

Experiment Participants The study reported in this article involved human participants, and as such we obtained approval for administration of study protocols from the Internal Review Board of the large Mid-Atlantic University at which we conducted the study. We obtained informed consent from all participants before administration of study protocols.

variable that can be used to identify people who evidence a particularly strong link between use of safety behaviors and expressing social anxiety.

Keywords

Adolescents; Social anxiety; Safety behaviors; Taq1A; BDNF

Adolescence is a critical time period of development. Many disorders have their onset in adolescence, particularly disorders with biological underpinnings (Paus et al. 2008) including social anxiety disorder. Intervening in social anxiety at an early stage is critical because the disorder tends to precede other mental disorders, such as depression and substance use (Beesdo et al. 2007; Marmorstein 2012). To treat social anxiety disorder, researchers often recommend interventions focused, in part, on exposing patients to anxiety provoking social situations (Kendall et al. 2006), yet not all patients respond well to this treatment (Hedtke et al. 2009). One group of treatment non-responders includes individuals who use behaviors to minimize distress within social situations (e.g., *safety behaviors*; Hedtke et al. 2009). It is possible that the extent to which a person evidences a strong link between their level of social anxiety and their use of safety behaviors may be moderated by individual differences, namely biological factors tied to expressions of anxiety.

As the field of psychology begins to incorporate multiple factors of etiology into research and treatment for mental disorders (e.g., Insel et al. 2010), investigating biological factors such as genetic individual difference variables linked to social anxiety and safety behaviors may usefully inform methods for personalizing treatments to optimize treatment response (for a review, see De Los Reyes and Aldao 2015). In fact, there is a growing body of studies investigating genetic factors as moderators of psychological phenomena (e.g., Bau et al. 2000; Belsky and van IJzendoorn 2015; Caspi et al. 2002; Mandelli and Serretti 2013). Further, the use of genetic moderation, which may distinguish groups who are more or less vulnerable to situational factors (e.g., social stress) depending on their genes, is supported by the theory of differential susceptibility to environmental influences (Belsky and Pluess 2009). Specific to anxiety, much of this work is informed by neurobehavioral models such as *Reinforcement Sensitivity Theory* (Gray 1970, 1976; Corr 2004, 2008; Gray and McNaughton 2000). *Reinforcement Sensitivity Theory* posits that variations in neurobiological risks for anxiety (e.g., allelic risk factors for anxiety) underlie individual differences in the expression of stable traits of personality related to anxiety (Eysenck 1990). In line with this prior research and theory, the purpose of this study is to investigate the extent to which an individual difference allelic risk factor linked to anxiety moderates the relation between social anxiety symptoms and use of safety behaviors.

Safety Behaviors and Social Anxiety

Social anxiety disorder is characterized by a fear of evaluation or embarrassment in social or performance situations (American Psychiatric Association 2000, 2013). Socially anxious individuals express these fears behaviorally by avoiding social situations, or otherwise enduring these situations with intense distress. The cognitive model of social anxiety (Clark and Wells 1995) posits a cycle that begins with an individual's negative beliefs about their

social abilities and social world, and that is maintained by safety behaviors, internal focus, and negative attributions. These factors impact the individual's behavior in social situations and as a result, may elicit negative reactions from other people, further contributing to this cycle of social anxiety and providing evidence of their (perceived) lack of social ability. Thus, social anxiety is broadly characterized by increased negative affect (Watson et al. 2005) and a heightened self-focused attention (Bögels and Mansell 2004; Mathews and MacLeod 2005).

The nature and extent of safety behavior use have important implications for the development, maintenance, and treatment of social anxiety (Clark and Wells 1995; Morrison and Heimberg 2013). Socially anxious individuals may engage in a variety of safety behaviors in order to reduce the acute distress they experience in social situations (e.g., Salkovskis 1991; Wells et al. 1995), and often in an attempt to avoid evaluation from others before or during feared situations (Cuming et al. 2009; Kashdan et al. 2011). According to Helbig-Lang and Petermann (2010, pgs. 219–220):

> Safety behaviors are dysfunctional emotion regulation strategies. They can be differentiated from adaptive coping depending both on the situation in which they occur (actual threat versus overrated or no real threat) as well as their function (preventing feared outcomes that are unlikely to happen versus habitual behavior or behavior unrelated to the occurrence of anxiety).

Examples of safety behaviors relevant to social anxiety include avoiding eye contact, saying as little as possible, wearing clothes that conceal signs of physiological arousal (e.g., baggy clothes to mask sweating), and privately rehearsing beforehand what to say in a situation. These behaviors may temporarily alleviate socially anxious individuals' negative thoughts and physiological experiences (e.g., perspiration and increased heart rate), but tend to maintain anxiety over time (Lovibond et al. 2009). In fact, the use of safety behaviors has an acute negative reinforcement property by leading to short-term reductions of discomfort in social situations (e.g., reduced distress as a function of avoiding speaking at a social gathering; Salkovskis 1991). Specifically, long-term use of safety behaviors (e.g., regularly refraining from mingling at social gatherings) may result in lost opportunities for disconfirmation of social fears, and thus, leads to increased risk for maintenance of social anxiety (see Thomas et al. 2012). Children and adolescents with social anxiety *disorder* exhibit a greater variety and higher rate of safety behaviors than socially anxious and non-anxious children and adolescents (Kley et al. 2012), providing evidence for the association between safety behaviors and social anxiety disorder (Clark and Wells 1995).

Findings from prior work in both youth and adults examining the outcomes of exposure-based treatments suggest 1) that some individuals use safety behaviors much more frequently than other individuals during exposure to social situations, and 2) the use of safety behaviors during exposures impedes treatment gains (Hedtke et al. 2009; Helbig-Lang and Petermann 2010; Kim 2005; Schmidt et al. 2012; Taylor and Alden 2010; Wells et al. 1995). Therefore, research strongly suggests that the use of safety behaviors by socially anxious individuals may represent a maladaptive coping strategy that prevents successful treatment of their symptoms and maintains corresponding impairments in social functioning.

Biological Bases for Links Between Social Anxiety Symptoms and Safety Behaviors

Thus, paradoxically, the use of safety behaviors appears to interfere with exposure-based treatment, and tends to result in a more negative impression to others in social situations—yet, individuals with social anxiety persist in using these strategies. Biological predispositions toward expressing features of social anxiety symptoms may serve to moderate the strength of links between social anxiety and safety behaviors. There is a robust literature underlying how genetic factors both impact the trajectory of the development of psychopathology and may even inform targeted interventions (Bau et al. 2000; Belsky and Pluess 2009; Belsky and van IJzendoorn 2015; Caspi et al. 2002; Hayden et al. 2010; Mandelli and Serretti 2013), and more specifically, supports the investigation of the biological bases for anxiety (e.g., Dillon et al. 2014; Flint 2004; Woody and Szechtman 2011). Influenced by these findings, we posit that investigating an individual differences variable of anxiety-related personality traits (Flint 2004; Kennis et al. 2013; McNaughton and Corr 2004, 2008) as a moderator may elucidate why the link between social anxiety and safety behaviors is strong for some adolescents and not others. In particular, personality is conceptualized here as the biological underpinnings of an individual's response to the environment (Allport 1937; Corr 2002; Davidson 2001), for which an individual's genetic make-up is known to make a substantial contribution (Eysenck 1990). In fact, the *Reinforcement Sensitivity Theory* provides a framework for a neurobehavioral etiology of anxiety, or an explanation for how anxiety-related behaviors are linked to biological systems of punishment and reward (Gray 1970, 1976; Corr 2004; Gray and McNaughton 2000). Specifically, allelic variation for dopamine as a genetic moderator both provides support for individual differences in expressions of anxious behavior (Freitas-Ferrari et al. 2010; Koven and Carr 2012; Schneier et al. 2000) and a potential illustration of how genes confer vulnerability to environmental factors like exposure to social situations (Belsky and Pluess 2009).

Allelic Variations Related to Social Anxiety

Two relevant allelic variation factors in the study of adolescent social anxiety and safety behaviors are the single nucleotide polymorphism (SNP) dopamine D2 receptor gene (DRD2/ANKK1 Taq1A rs1800497), and brain-derived neurotrophic factor gene SNP (BDNF rs6265). First, reduced dopaminergic functioning (i.e., decreased numbers of dopamine receptors) appears to be a factor related to social anxiety (Freitas-Ferrari et al. 2010; Gillath et al. 2008; Schneier et al. 2000; Stein et al. 2002). The polymorphism Taq1A (rs1800497) on the Anakin repeat transporter gene (ANKK1) next to the dopamine D2 receptor gene (see Dick et al. 2007; Neville et al. 2004) is associated with risk for anxiety (Hayden et al. 2010) and alcohol dependence (Blum et al. 1991; Preuss et al. 2007). Biologically, the presence of the A1 allele of Taq1A is associated with reduced dopamine receptors (Jönsson et al. 1999; Noble et al. 1991; Pohjalainen et al. 1998), and hypothesized to index difficulty coping with stress (Bau et al. 2000). For individuals carrying the A1 allele, the presence of this allele is related to characteristics of social anxiety. For example, relative to adolescents without the A1 allele, adolescents with the A1 allele undergoing

electroencephalography while completing a probabilistic learning task exhibited greater sensitivity to negative feedback and less focus on positive feedback on their task performance (Althaus et al. 2009). The presence of the A1 allele in a sample of children was significantly related to increased anxiety and depression, measured by both maternal report and structured interview (Hayden et al. 2010). Further, there is a significant link between carrying the A1 allele and increased social problems (Marino et al. 2004). In fact, individuals who carry one or both copies of the A1 allele appear to be at greater risk for concerns often linked with increased social anxiety and/or social problems (i.e., substance use problems), relative to individuals without the A1 allele (Berggren et al. 2006; Huang et al. 2009; van der Zwaluw et al. 2010; van der Zwaluw et al. 2011).

Second, and also linked to dopaminergic pathways, BDNF is a nerve growth factor protein related to neural plasticity (Berton et al. 2006; Guillin et al. 2001; Hyman et al. 1991; Seroogy et al. 1994). Of relevance to social anxiety, allelic variations of BDNF tend to relate with variations in functional impairments in the domains of fear-related learning, memory, and extinction (Casey et al. 2011; Soliman et al. 2010; Yu et al. 2009). The BDNF SNP Val66Met (rs6265) has two alleles (Methionine [Met], Valine [Val]), comprising 3 genotypes: Val/Val, Val/Met, and Met/Met. The Met allele has been linked to stress reactivity, mood and anxiety disorders and related behaviors (Chen et al. 2006; Colzato et al. 2011; Duman and Monteggia 2006; Gadow et al. 2009; Jiang et al. 2005; Verhagen et al. 2010), alcohol dependence (Su et al. 2011), smoking behavior (Lang et al. 2007), memory (Egan et al. 2003; Yu et al. 2009), and introversion (Terracciano et al. 2008, 2009; Stein and Gelernter 2010), many of which also relate to social anxiety. In a sample of young adults completing a stressor task (i.e., cold pressure task), carriers of the Met allele, relative to the Val/Val genotype, experienced greater nervousness, social anxiety, stress response and weekly alcohol consumption (Colzato et al. 2011). Given BDNF's association with risk for anxiety and sequelae (e.g., addiction), and its possible influence on the ability to learn the difference between safety and threat (Casey et al. 2010), it is an important gene to study in relation to social anxiety.

Present Study

The purpose of this study was to advance knowledge on the influence of an individual difference allelic risk factor on the relation between social anxiety symptoms and safety behaviors in adolescents. Specifically, we applied research and theory on allelic variations related to anxiety symptoms to improve our understanding of individual differences in the strength of relations between adolescent social anxiety and safety behaviors. One way to investigate the risk for social anxiety is to create a dichotomous variable indexing allelic variation related to neurotransmitters germane to anxiety, namely dopamine (see Conner et al. 2010). Allelic variation variables are often used in other fields of study in the general medical sciences (e.g., to examine breast cancer, gout, and heart disease; Aulchenko et al. 2009; Dehghan et al. 2008; De Jager, et al. 2009; Jacobsen et al. 1997; Kathiresan et al. 2008; Morrison et al. 2007). We expected that high levels of social anxiety would be related to high usage of safety behaviors, and that this relation would be moderated by the presence of allelic variation for anxiety symptoms. Specifically, we hypothesized that adolescents carrying allelic variation for anxiety symptoms would evidence a stronger positive

association between social anxiety symptoms and safety behaviors, relative to adolescents carrying no such allelic variation.

Method

Participants

Participants were families who lived in a large metropolitan area in the Mid-Atlantic United States. In order to participate in the study, families had to: (a) speak English fluently, (b) understand the consent and assent process, (c) have an adolescent currently living in the home whom the parent did not report as having a history of learning or developmental disabilities, and (d) have an adolescent and parent present for the assessment. Seventy-nine families participated in the study; however, four families were excluded from the analyses because either the adolescent did not provide sufficient saliva to assess the two allelic variation variables described below or did not provide proper survey measure data. Recent studies using sampling approaches similar to our own support the use of samples of this size in genetics research (e.g., Althaus et al. 2009; Anderson et al. 2012; Beevers et al. 2007; Carlson et al. 2012; Mueller et al. 2013; Way and Taylor 2011).

Thus, the analytic sample of 75 families included adolescents aged 14-to-17 years (32 males and 43 females; *M* age= 15.37 years [*SD*=1.09]). The parents identified family ethnicity/race as African American or Black (64.9 %); White, Caucasian American, or European (28.4 %); Hispanic or Latino/a (4.1 %); Asian American (2.7 %); American Indian (2.7 %); or “Other” (three [4.1 %] participants entered “Bi-Racial,” “Indian,” and “Jewish”; one participant did not report ethnicity/race data). The composition of family ethnicity/race totals above 100 % because there was overlap among the ethnic/racial categories, resulting from participants having the option of selecting more than one ethnic/racial category. Based on parent report, over one quarter (28.8 %) of the families had a weekly household income of $500 or less; 49.3 % earned $901 or more per week (two participants did not provide income data).

The 75 families participating in this study were recruited from two larger studies, conducted at the same time and recruited from the same geographic location, that focused on measurement of family relationships (e.g., parent-adolescent conflict; see De Los Reyes et al. 2012b) or adolescent social anxiety (e.g.,De Los Reyes et al. 2012a). Specifically, 36 adolescents had a parent who contacted the laboratory in response to an advertisement for a non-clinic study about family relationships. Additionally, we augmented the sample by including 39 adolescents who had a parent who contacted the laboratory in response to an advertisement for a social anxiety clinical screening evaluation. We included these adolescents to increase variability in the assessment of adolescent safety behaviors, consistent with prior work (see Thomas et al. 2012), thus increasing our statistical power to detect hypothesized effects. Importantly, demographic comparisons of these two samples of adolescents yielded no significant differences on any of the demographic characteristics reported previously (i.e., adolescent age, adolescent gender, family ethnicity/race, and family income, all *ps*>.11). Similarly, the two samples did not significantly differ on frequency distributions for the genetic allele variations reported below (i.e., DRD2/ANKK1, and BDNF), *ps*>.11. In sum, these samples did not significantly differ on demographic

characteristics and genetic allele variation frequencies, thus providing a justification for combining them to address our study aims.

Procedure

All procedures were approved by the Internal Review Board of the large Mid-Atlantic university at which the study was conducted. We recruited participants through community agencies and events, as well as via advertisements posted online (e.g., Craigslist) and in newspapers in qualifying neighborhoods (i.e., neighborhoods targeted because of demographic and income variability). Additionally, we recruited participants who were referred for social anxiety evaluations through the offices of pediatricians, mental health professionals, and other health care providers.

After respondents were screened for eligibility over the telephone, we scheduled them for an assessment. After the parents provided written consent and the adolescents provided assent, adolescents provided a saliva sample for the genotyping analyses described below. Participants were then led to a separate room to complete a counterbalanced battery of assessments via individual computer-based questionnaires. Specifically, for all survey assessments, participants provided computer-based responses to items that were recorded using IBM SPSS Data Collection survey administration software (Version 5.6; IBM Corporation 2009). Following completion of the study, participants were debriefed as to the overall goals of the study and monetarily compensated for their time.

Measures

Adolescent and Parent Survey Measures—Adolescents and parents completed measures assessing domains of adolescent and family demographics, adolescent social anxiety, and adolescent safety behaviors:

Adolescent and family demographics: Demographic data were obtained through parent reports of child age and gender, family/ethnicity/race, and family income.

Self-reports of adolescent social anxiety concerns: We assessed adolescent self-reported social anxiety using the Multidimensional Anxiety Scale for Children (MASC; March 1997), a 39-item scale that assesses various domains of anxiety functioning in youths: physical symptoms, harm avoidance, social anxiety, and separation anxiety/panic. Adolescents rated each symptom on a scale from 0 (*Never true about me*) to 3 (*Often true about me*). Total scores can range from 0 to 117, with higher scores reflecting greater anxiety symptoms. The MASC has been used extensively, with strong evidence for its reliability and validity (March 1997; Silverman and Ollendick 2005). For the current study, we examined the nine-item Social Anxiety subscale, which yielded a high internal consistency estimate for the sample, α=.88.

Self-reports of adolescent safety behaviors: Use of safety behaviors was assessed by having the adolescents complete the Subtle Avoidance Frequency Examination (SAFE; Cuming et al. 2009). The SAFE is a 32-item scale originally developed for adults that assesses subtle safety-seeking behaviors that an individual may use prior to or during a

social situation. Adolescents rated each item by determining how often they would engage in the behavior if they were in a social situation by using a scale from 1 (*Never*) to 5 (*Always*). Total scores can range from 32 to 160, with higher scores reflecting greater use of safety behaviors. The SAFE distinguishes clinical (i.e., social anxiety disorder patients) from non-clinical adult samples and evidences high construct validity (Cuming et al. 2009). Additionally, a recent age- and gender-matched case-control study of socially anxious and non-socially anxious adolescents supported the internal consistency discriminant, and convergent validity of the SAFE when administered to adolescents, most of which are included in the current study (Thomas et al. 2012). Specifically, the SAFE correlated significantly with the MASC (r=.49) and exhibited low-to-moderate, non-significant correlations with measures related to attention/hyperactivity symptoms and depression. Further, the SAFE successfully distinguished referral status in the sample by differentiating between adolescents referred for anxiety concerns from adolescents recruited for a study on family behavior (Thomas et al. 2012). The SAFE yielded a high internal consistency estimate for the current sample, α =.90. Sample items in which adolescents rate how often they engage in safety behaviors include “Speak softly” and “Hold your arms still”.

Genetic Analysis—Through the sampling procedures described below, we assessed for the presence of multiple gene alleles which previous work indicates are associated with anxiety symptoms.

Saliva sampling and storage: Adolescent participants provided a single saliva sample via a sublingual Salimetrics© (State College, PA) oral cotton swab (Part No. 5001.02). Specifically, study personnel instructed the adolescents to hold the swab under their tongue for two minutes' time, and to deposit the swab into a plastic vial (Salimetrics© swab storage tube, Part No. 5001.05), within which the swab remained for storage. This is in line with the manufacturer's instructions. We stored saliva samples in a Biomedical Solutions Incorporated Upright Freezer (Model SCGP17OW1AF) before packaging and shipping the samples in dry ice for genetic extraction and analysis.

Genetic extraction and analysis: Extraction and analysis of genetic information was performed by personnel at the Salimetrics© laboratory (State College, PA). Specifically a modified Puregene (Gentra) extraction method was used to isolate the DNA from the saliva samples we provided. The samples were treated with Cell Lysis Solution (Qiagen) and Proteinase K and then incubated. After cell lysis, the samples were treated with Protein Precipitation Solution and then centrifuged. The supernatant was removed and samples were treated with Isopropanol to precipitate the DNA. Finally, the samples were washed to remove any remaining impurities, and the DNA was suspended in Nuclease Free Water. Following this, a GE NanoVue Spectrophotometer was used to measure the absorbance of the purified DNA, and to determine the quantity and quality of nucleic acid recovered in each sample. A Taqman Genotyping Assay (Applied Biosystems) was employed to amplify and evaluate the DRD2/ANKK1 and BDNF alleles described below.

DRD2/ANKK1: To assess for gene allele variation for social anxiety characteristics, we assessed for genotype frequencies on the DRD2/ANKK1 Taq1A rs1800497 gene. In line

with previous work (e.g., Preuss et al. 2007), we assessed for the presence of the A1 allele. Specifically, we identified adolescents who were either homozygous (A1/A1) or heterozygous for A1 (A1/A2), hereafter referred to as "A1+". There were 6 adolescents with the A1/A1 genotype, 26 adolescents with the A1/A2 genotype, and 43 adolescents with the A2/A2 genotype. The measured genotype frequencies corresponded to the Hardy-Weinberg equilibrium (N=78, χ^2=0.88, df=1, p=346).

BDNF: To assess for gene allele variation for fear-related learning, memory, and extinction, we assessed for genotype frequencies on the BDNF rs6265 gene. Consistent with prior research (Colzato et al. 2011; Gadow et al. 2009; Lang et al. 2007), we identified participants with the Met allele (i.e., Val/Met or Met/Met; hereafter collectively referred to as "Met+"). There were 6 adolescents with the Val/Met genotype, 2 adolescents with the Met/Met genotype, and 67 adolescents with the Val/Val genotype. The measured genotype frequencies were not in Hardy-Weinberg equilibrium (N=77, χ^2=9.88, df=1, p=.002), which could be due to the rarity of the Met/Met genotype (Shimizu et al. 2004).

Allelic variation: We were interested in identifying allelic variation for dopaminergic effects on social anxiety which involved identifying adolescents who were A1+ (n=32) and/or Met+(n=8). From these allele variation frequencies, we calculated a dichotomous allelic variation score (Conner et al. 2010), based on whether an adolescent carried a risk on either of the two alleles (n=38) or carried no risk (n=37). We considered creating a count variable with a possible range of 0-to-2 but decided against it because only 2 adolescents carried allele variation for more than one gene, thus limiting our statistical power to detect interaction effects using a range of 0-to-2.

Data-Analytic Plan

We first conducted preliminary analyses to detect deviations from normality. We also computed bivariate correlations between our main independent and dependent variables. Further, we conducted independent samples *t*-tests to compare allele variation conditions on safety behavior usage and social anxiety symptoms. These univariate tests allowed us to examine the utility of an allelic risk score for interpreting scores on a well-established measure of social anxiety (i.e., MASC Social Anxiety subscale), as well as our criterion variable measure of safety behaviors (i.e., the SAFE). To test our main hypothesis, we conducted a hierarchical regression analysis in which the adolescent SAFE total scores served as the criterion variable. We entered child age (centered) and gender (coded "0" for male and "1" for female) in the first step as independent variables. In the second step, we entered as independent variables the MASC Social Anxiety scores (centered) and a dichotomous variable representing the presence (coded "1") or absence (coded "0") of any of the aforementioned allelic variations for DRD2/ANKK1 and BDNF. In the third step, we entered the interaction term for the MASC Social Anxiety scores and allelic variations scores. In the presence of a significant interaction effect, we used Holmbeck's (2002) guidelines for post-hoc probing of significant moderator effects. This included: (a) computation of slope estimates using centered variables (reducing multicollinearity) and (b) examining the statistical significance of these slopes for the presence versus absence of allelic variations for anxiety symptoms (i.e., the moderator variable).

Importantly, the general cognitive model of social anxiety posits that symptoms and maladaptive behaviors are often cyclical (e.g., increased social anxiety prompts increased use of safety behaviors, eliciting negative reactions from other individuals in the interaction, thus increasing social anxiety; Clark and Wells 1995). Thus, consistent with the bidirectional relations between safety behaviors and social anxiety, we constructed a second hierarchical regression in which the MASC Social Anxiety scores served as the criterion variable and we entered SAFE total scores (centered) as an independent variable. All other independent variables, regression equation steps, and processes for testing interaction effects remained the same as the first equation described previously.

Results

Preliminary Analyses

Continuous Variables—The MASC Social Anxiety score (M=12.02; SD=6.46) and the SAFE total score (M=72.61; SD= 19.02) both met the statistical assumptions for the analyses (i.e., acceptable ranges of skewness and kurtosis statistics [≈ +/−1.0]). Consistent with prior work (Cuming et al. 2009), the MASC Social Anxiety score and the SAFE total score correlated in the moderate-to-large range, r=.52, p<.001 (Cohen 1988).

Univariate Analyses—To compare social anxiety scores and safety behavior scores in adolescents with and without allelic variation for anxiety symptoms, we conducted independent samples t-tests. There were no significant differences on scores of safety behavior use ($t(73)$=−1.26, p=.21) for adolescents with (M=75.34, SD=20.03) and without allelic variation for anxiety (M=69.81, SD=17.76). However, scores of social anxiety symptoms did significantly differ ($t(73)$= −2.47, p=.016, d=−0.58) between adolescents with allelic variation for anxiety (M=13.79, SD=6.61) and without allelic variation risk (M=10.21, SD=5.85). Importantly, the mean level of social anxiety symptoms we observed for adolescents with allelic variation of risk for anxiety (13.79) was in line with previously recommended clinical cutoffs for the MASC Social Anxiety scale (13.5; Wood et al. 2002).

Interaction Between Allelic Variations and Adolescent Social Anxiety Symptoms in Relation to Adolescent Safety Behaviors

Hierarchical regression analyses were conducted to test our main hypothesis. In Step 1, we observed non-significant effects for adolescent age and gender, $F(2, 72)$=0.41, p=.66. In Step 2, the main effect of social anxiety (b=1.51, SE=0.31, β=0.51, p<.001), but not the allelic variation score (b=0.11, SE=4.01, β=0, p=.97), were significant, $F(4, 70)$=6.60, p<.001. Consistent with our hypothesis, as presented in Table 1, in Step 3 we observed a significant interaction between the dichotomous allelic variation score and the MASC Social Anxiety scale score in relation to the SAFE total score. As seen in Table 1, this interaction explained variance in the relation between social anxiety symptoms and safety behaviors over the unique contributions of the independent variables, $F(5, 69)$=6.81, p<.001. Graphically depicted in Fig. 1, post-hoc probing analyses revealed that adolescents carrying allelic variations for anxiety evidenced a statistically significant and relatively strong positive relation between the MASC Social Anxiety scale score and the SAFE total score,

whereas adolescents who did not carry allelic variation of risk for anxiety symptoms evidenced a statistically non-significant and relatively weak relation (see also Table 1).[1]

As shown in Table 2, when the criterion variable was the MASC social anxiety subscale and we tested the interaction between allelic variation and the SAFE total score, the interaction effect was also significant. Specifically, in Step 1 we observed non-significant effects for adolescent age and gender, $F(2, 72)=0.19$, $p=.82$. In Step 2, the main effects of both SAFE total score ($b=0.16$, $SE=0.03$, $\beta=0.48$, $p<.001$) and the allelic variation score ($b=2.67$, $SE=1.29$, $\beta=0.21$, $p=.04$) were significant, $F(4, 70)=7.93$, $p<.001$. In Step 3, both the main effect of the allelic variation score and the interaction between the dichotomous allelic variation score and the SAFE total score in relation to MASC Social Anxiety scale score were significant, $F(5, 69)=7.83$, $p<.001$. Post-hoc probing analyses indicated that adolescents carrying allelic variations for anxiety evidenced a statistically significant and relatively strong positive relation between the SAFE total score and the MASC Social Anxiety scale score, whereas adolescents who did not carry allelic variation of risk for anxiety symptoms evidenced a statistically non-significant and relatively weak relation (see Table 2).

Discussion

Main Findings

The purpose of this study was to extend the literature on adolescent safety behaviors and adolescent social anxiety symptoms. In a sample of adolescents enriched for variability in social anxiety and safety behaviors, we advanced the literature by incorporating recent work on allelic variations of risk for anxiety symptoms and examining how individual differences on alleles relevant to anxiety moderate the relation between social anxiety and use of safety behaviors. Consistent with prior research and theory related to anxiety (Colzato et al. 2011; Hayden et al. 2010; Wells et al. 1995) and genetic moderators of psychopathology (e.g., Bau et al. 2000;Belsky and van IJzendoorn 2015; Caspi et al. 2002; Mandelli and Serretti 2013), allelic variation of risk for anxiety symptoms moderated this relation such that we observed a large-magnitude and positive relation between social anxiety symptoms and safety behaviors, but only for those adolescents carrying allelic variation for anxiety symptoms. Interestingly, the average MASC social anxiety score for adolescents carrying the allelic variation of risk for anxiety symptoms was slightly above previously reported clinical cutoffs for the MASC social anxiety scale (Wood et al. 2002), thus corroborating our use of the allelic variation score in this study.

Limitations

Conducting psychological research involving genes is a developing area for which recommendations have recently been developed (Johnston et al. 2013). Along those lines, this study had several limitations. First, the sample size was relatively low compared to other studies on genetic correlates of risk. Although we were well-powered to detect our

[1]Prior work indicates that allele frequencies may covary with ethnicity in the general population. In our current study, ethnicity did not explain any variance in the criterion variable ($F[2, 72]=0.19$, $p=.827$) and thus was excluded from all analyses.

hypothesized effects, our sample size nonetheless may have contributed to BDNF genotype frequencies not corresponding to the Hardy-Weinberg equilibrium (e.g., Wittke-Thompson et al. 2005), particularly since the Met/Met genotype is rare (Shimizu et al. 2004). Importantly, our sample size is in line with some recent work taking an enriched sampling approach similar to our own (i.e., patients and non-clinic participants from the community) to study genes related to individuals with clinical disorders (Althaus et al. 2009; Anderson et al. 2012; Beevers et al. 2007; Carlson et al. 2012; Mueller et al. 2013; Way and Taylor 2011). Second, Taq1A and BDNF have been associated with several psychological domains besides anxiety, such as memory and depression (Duman and Monteggia 2006; Egan et al. 2003). At the same time, the genes we investigated are both linked to the regulation of dopamine in the brain, which has been implicated in the development and maintenance of anxiety concerns (Freitas-Ferrari et al. 2010; Gillath et al. 2008; Schneier et al. 2000; Stein et al. 2002). Further, both genes have extensive empirical support for their relation to symptoms related to social anxiety, in line with recommendations for genetic research (Johnston et al. 2013).

Third, our survey measures were administered via self-report. One recommendation regarding gene-environment interactions is to use separate informants to assess independent and criterion variables (Johnston et al. 2013). However, in light of the often-covert nature of safety behaviors and social anxiety symptoms, our findings might not generalize to measurements based on observers' reports (e.g., parents and teachers; see De Los Reyes 2013; De Los Reyes et al. 2015; De Los Reyes et al. 2013). Fourth, and similarly, although we assessed multiple allele variations in this study, it is likely that many other genetic expressions relate to safety behaviors and social anxiety symptoms. Therefore, we encourage future research to extend our findings using study designs that are multi-informant, multi-allele, and wherever possible, prospective, in order to monitor how genetic factors may relate to the development of other maladaptive coping strategies similar to safety behaviors.

Implications for Clinical Research and Practice

Biological Underpinnings of Social Anxiety—Results from the present study support the utility of investigating the biological underpinnings of social anxiety. Indeed, this work may inform future research on the identification of key intervention targets that facilitate reductions in anxiety-related impairments (see also De Los Reyes and Aldao 2015). The genetic polymorphisms we investigated have links to social anxiety characteristics, and only those adolescents with the presence of the allelic risk exhibited a significant relation between social anxiety and safety behaviors. These findings further support current initiatives for investigating multiple domains of functioning and their links with psychopathology (e.g., Research Domain Criteria; Insel et al. 2010), as well as provide further support for biological factors linked to anxiety-related behavior. As mentioned previously, the genotypes we examined in this study are related to other mechanisms such as number of dopamine receptors and activity in brain regions linked to social anxiety. This suggests promising future directions for further investigation into what aspects of these allelic risks may be encoding for the strong link between social anxiety and safety behaviors. It is possible that these biological factors pose risk for the development of cognitive and

behavioral symptoms of social anxiety, and may also make typical exposure treatment less successful. However, these notions are speculative and thus merit further study.

Treatment of Social Anxiety Disorder in Adolescents—Our findings have two important implications for treating adolescent social anxiety. First, a large body of literature supports the efficacy of exposure-based treatments for reducing adolescent social anxiety symptoms (e.g., Alfano and Beidel 2011). However, when children and adolescents engage in safety behaviors during behavioral exposures administered during these treatments, this predicts poor treatment outcomes (see Hedtke et al. 2009). Conversely, treatment research indicates that eliminating use of safety behaviors during exposures results in decreased social anxiety (Kim 2005; Taylor and Alden 2010; Wells et al. 1995). Thus, it is possible that assessing safety behaviors regularly in adolescents presenting with social anxiety may provide an indicator of possible maladaptive coping, which could be a potential target in treatment for social anxiety.

Second, and of direct relevance according to our findings, a biological characteristic that may impact exposure treatment is the allelic risk association with fear-related learning and memory. To illustrate, research on Taq1A suggests that during a probabilistic learning task, individuals with the A1 allele have difficulty learning from the negative results of their responses to stimuli in order to modify their future responses (Klein et al. 2007). Thus, individuals with the Taq1A allele may be less likely to observe and modify their behavior when their coping strategies are not working—which could include the use of safety behaviors to ameliorate distress. Prior studies have been successful in developing targeted psychosocial interventions based on genetic profiles, so this suggests a possible future avenue of research with this population (Belsky and van IJzendoorn 2015; Brody et al. 2009).

Prevention of Conditions that Co-Occur with Social Anxiety—It is important to note that both of the genotypes investigated in the present study also have links to concerns that commonly co-occur with social anxiety, namely substance use (Berggren et al. 2006; Blum et al. 1991; Colzato et al. 2011; Huang et al. 2009; Preuss et al. 2007; Su et al. 2011; van der Zwaluw et al. 2010; van der Zwaluw et al. 2011). Understanding the relation between safety behaviors and social anxiety, and how allelic variation may moderate this relation, may help prevent substance use in adolescence from developing into substance use disorders. This is particularly important given the fact that substances such as alcohol have been associated with short-term reductions in anxiety in feared situations (Abrams et al. 2001; Battista et al. 2012), which could potentially lead to a pattern of increasing usage over time. Given the strong association between social anxiety and substance use, and the temporal ordering of the two disorders (i.e., social anxiety tends to precede substance use; Marmorstein 2012), intervening during adolescence may be essential in preventing future substance problems.

Concluding Comments

The present study sought to investigate the moderating effects of allelic variation of risk for anxiety symptoms on the association between adolescent social anxiety and safety

behaviors. We observed a large-magnitude and positive relation between adolescent social anxiety symptoms and safety behaviors, but only for adolescents carrying an allelic variation for anxiety symptoms. These findings have important implications for identifying adolescents at risk for experiencing reduced response to exposure-based treatments for social anxiety. Given the impairment in functioning associated with developing social anxiety disorder, the assessment of safety behaviors in adolescents with social anxiety may be a salient starting point to investigate and determine maladaptive coping behaviors.

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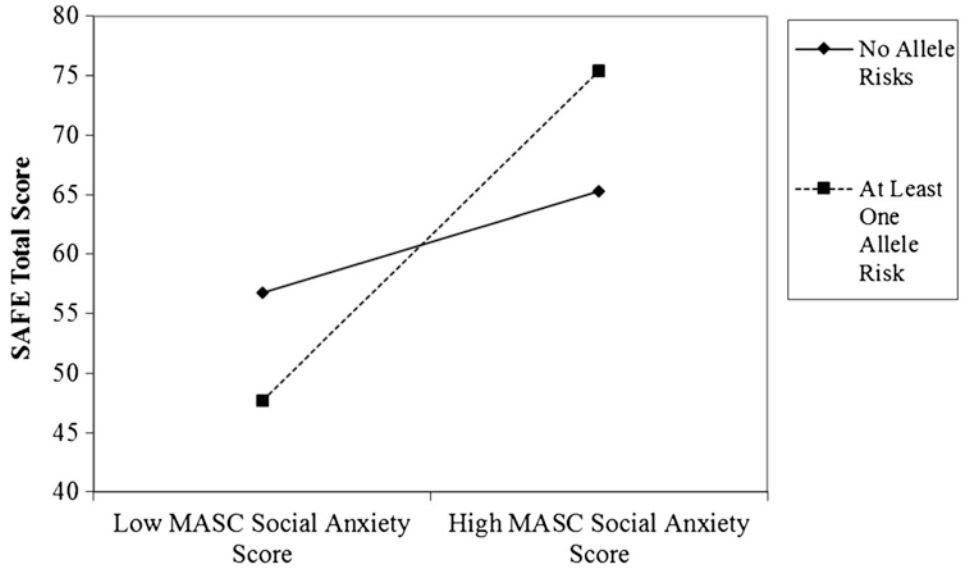

Fig. 1.

Interaction effect between Multidimensional Anxiety Scale for Children (MASC) Social Anxiety scale scores and allelic variation of risk for anxiety symptoms, positively relating to Subtle Avoidance Frequency Examination (SAFE). Post-hoc probing analyses indicated that adolescents carrying at least one allele risk experienced positive relations between MASC Social Anxiety scale scores and SAFE total scores (see Table 1)

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Table 1

Hierarchical regression analyses examining the interaction between allelic variation of risk for anxiety symptoms and adolescent safety behaviors in relation to adolescent social anxiety symptoms

Main regression model					**Post-hoc tests of moderation**				
Variable	**ΔR^2**	***B***	***SeB***	***β***	**Variable**	**ΔR^2**	***B***	***SeB***	***β***
Step 1	0.01				Step 3 (when “0” = at least one allele risk)	0.05*			
Adolescent age		−0.33	1.73	−0.02	Allele risk score		0.54	3.88	0.01
Adolescent gender		3.48	3.81	0.09	MASC social anxiety score		2.14	0.40	0.73**
Step 2	.26**				Allele risk × MASC social anxiety score		1.48	0.61	0.32*
Allele risk score		0.54	3.88	0.01					
MASC social anxiety score		0.66	0.46	0.22	Step 3 (when “0” = no allele risk)	.05*			
Step 3	0.05*				Allele risk score		0.54	3.88	0.01
Allele risk × MASC social anxiety score		1.48	0.61	0.37*	MASC social anxiety score		0.66	0.46	0.22
					Allele risk × MASC social anxiety score		1.48	0.61	0.37*

For the main regression model (left side of table), regression terms for variables entered at steps 1, 2, and 3 are displayed, based on terms observed for these variables in step 3 of the model; ΔR^2 statistics for each step were based on variables entered in that step; for the post-hoc moderation tests (right side of table), only Step 3 is reported, with the moderator variable (i.e., allele risk) manipulated to reflect instances in which “0” equaled “at least one allele risk”, and instances in which “0” equaled “no allele risk”) (see Holmbeck 2002); *MASC* Multidimensional Anxiety Scale for Children

* $p<.05$;

** $p<.001$

Table 2

Hierarchical regression analyses examining the interaction between allelic variation of risk for anxiety symptoms and adolescent social anxiety symptoms in relation to adolescent safety behaviors

Main regression model					**Post-hoc tests of moderation**				
Variable	**ΔR^2**	***B***	***SeB***	***β***	**Variable**	**ΔR^2**	***B***	***SeB***	***β***
Step 1	0				Step 3 (when “0” = at least one allele risk)	0.05*			
Adolescent age		−0.05	0.57	−0.01	Allele risk score		2.72	1.25	0.21*
Adolescent gender		0.40	1.26	0.03	SAFE total score		0.23	0.04	0.68**
Step 2	0.30**				Allele risk × SAFE total score		0.15	0.06	0.30*
Allele risk score		2.72	1.25	0.21*					
SAFE total score		0.07	0.05	0.22	Step 3 (when “0” = no allele risk)	0.05*			
Step 3	0.05*				Allele risk score		2.72	1.25	0.21*
Allele risk × SAFE total score		0.15	0.06	0.34*	SAFE total score		0.07	0.05	0.22
					Allele risk × SAFE total score		0.15	0.06	0.34*

For the main regression model (left side of table), regression terms for variables entered at steps 1, 2, and 3 are displayed, based on terms observed for these variables in step 3 of the model; ΔR^2 statistics for each step were based on variables entered in that step; for the post-hoc moderation tests (right side of table), only Step 3 is reported, with the moderator variable (i.e., allele risk) manipulated to reflect instances in which “0” equaled “at least one allele risk”, and instances in which “0” equaled “no allele risk”) (see Holmbeck 2002); *SAFE* Subtle Avoidance Frequency Examination

* $p<.05$;

** $p<.001$

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