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Interaction Effects between the Cumulative Genetic Score and Psychosocial Stressor on Drinking Urge and Attentional Bias for Alcohol: A Human Laboratory Study

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Abstract

Stressful life events have been positively associated with alcohol use and misuse in young adults; however, individual differences in the association suggest the presence of moderators. Findings from observational studies suggest that the effects of stressful environments on drinking behavior may differ as a function of diverse single monoamine genes regulating serotonin and dopamine neurotransmission. However, research has not utilized an experimental design to examine whether the monoamine genes collectively are associated with the degree to which exposure to stressors affects alcohol endophenotypes. The current study examined whether the effects of an experimentally manipulated psychosocial stressor on drinking urge and attentional bias for alcohol cues differ as a function of the cumulative genetic index of *5-HTTLPR*, *MAO-A*, *DRD4*, *DAT1*, and *DRD2* genotypes (candidate genes and environment interaction; cGxE). The current study also examined whether salivary alpha-amylase level or anxiety state mediate the cGxE effects. One hundred five Caucasian young adults (mean age = 19.83; 61% male) went through both control and experimental stress conditions in order. Results showed that, as the cumulative genetic score of the five monoamine genes increased, attentional bias for alcohol-related stimuli elevated in the stress condition but not in the control condition. No mediating roles of salivary alpha-amylase and anxiety state in the cGxE effect were found, however. High cumulative genetic score of the five monoamine genes was associated with elevated drinking urge both in the control and stress conditions. Although replication is necessary, the findings suggest that the five monoamine genes collectively were positively associated with the cognitive process of an individual's drive for alcohol (i.e., attentional bias) in stressful situations. The underlying psychological and neurobiological mechanisms need to be further characterized.

Keywords: gene-environment interaction, cumulative genetic score, stressor, drinking urge

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끊임없는 지지와 사랑으로 부인의 학위를 위해 오랜 기간동안 많은 희생을 감당해준 남편 이수용님께 이 박사논문을 바칩니다

Table of Contents

List of Tables

Tables Page

List of Figures

Figures Page

Interaction Effects between the Cumulative Genetic Score and Psychosocial Stressor on Drinking Urge and Attentional Bias for Alcohol: A Human Laboratory Study

Exposure to stressors have been consistently associated with a greater risk of alcohol misuse (Dawson, Grant, & Ruan, 2005; King, Bernardy, & Hauner, 2003) and a higher rate of alcoholism (Catalano, Dooley, Wilson, & Hough, 1993; Fox, Bergquist, Hong, & Sinha, 2007; Noone, Dua, & Markham, 1999). Stress response dampening theory (Sher, 1987) maintains that individuals in stressful situations drink alcohol to reduce their stress, and as they are exposed to stressful situations repeatedly, their drinking behavior is reinforced by its short-term stress reducing effects. Among young adults, drinking to cope with stress has been associated with greater drinking problems as compared to other reasons to drink (e.g., mood enhancement and social reasons) (for a review, see Kuntsche, Knibbe, Gmel, & Engels, 2005).

Drinking behavior is not only driven by environmental factors (such as stressful environments) but also genetic factors. Twin studies demonstrate that 14% to 55% of individual differences in drinking are explained by genetic factors, although the proportion of genetic influences on drinking varies based on age and the specific alcohol phenotype under examination (Geels et al., 2012). Although drinking behavior is thought to be influenced by numerous genes, there is a growing literature about the important role of monoamine genes in the production, secretion, and regulation of dopamine, serotonin, and norepinephrine in the brain and peripheral nervous system. Monoamine neurotransmitters have been shown to play a role in alcohol appetite, alcohol withdrawal symptoms, and development of tolerance in animal and human studies (for a review, see Nutt & Glue, 1986). Particularly, *5-HTTLPR, DRD4, DAT1, DRD2*, and *MAO-A* monoamine genotypes have been frequently studied and have shown to be associated with alcohol use and misuse, as described in detail below. In a large national study of young adults (n = 2,466; Guo, Wilhelmsen, & Hamilton, 2007), these

five monoamine genes individually accounted for 7-20% of individual differences in drinking frequency.

More importantly, accumulating evidence suggests that these monoamine genes may modify the associations of stressful environments with drinking behavior. That is, monoamine genotypes may be associated with individuals' vulnerability to stressful environments, which in turn is associated with the likelihood of alcohol use or misuse. This line of candidate Gene and Environment interaction (cGxE) studies investigate whether an individual's genotypes strengthen or weaken their susceptibility to environmental influences (Caspi & Moffitt, 2006; Rutter, 2006). Certain environmental influences on drinking behavior may actualize only in individuals with greater genetic risk (Rende & Plomin, 1992). Candidate GxE studies depart from a deterministic point of view of nature versus nurture and rather emphasize the interplay between one's genetic characteristics and environmental exposures.

These cGxE studies are in line with diathesis stress model (Zuckerman, 1999) suggesting that some individuals have a predispositional vulnerability to stressful environments, and exposure to stressors triggers their underlying vulnerability. Recently, beyond the diathesis stress model, cGxE studies involving monoamine genotypes also showed growing evidence supporting the differential susceptibility hypothesis (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009). That is, individuals with certain monoamine genotypes may not be only more vulnerable to stressful environments, but also more susceptible to the beneficial effects of protective environments (or abstinence/lack of stressful environments).

Interaction Effects between Monoamine Genes and Stressful Environments on Drinking

The following sections describe the findings of cGxE studies examining interactions between individual monoamine genes (not cumulative genetic score) and stressful

environments on alcohol outcomes. All existing research has been observational and no experimental studies have been reported. Overall, there is considerable evidence to support associations of individual monoamine genes with alcohol use and misuse. However, some findings were not successfully replicated across studies, which is a main criticism of individual cGxE studies (Duncan & Keller, 2011) and showed some inconsistencies in either the significance of cGxE effects or the risk-conferring allele.

5-Hydroxy Tryptamine Transporter Linked Promoter Region (5-HTTLPR).

5-HTTLPR is found to modulate levels of transcriptional activity of the serotonin transporter. Allelic variations of the *5-HTTLPR* are located on chromosome 17q11.2 (Kranzler & Anton, 1994). Two meta-analyses reported that the positive association of the short allele (which was found to lower levels of transcriptional activity of the serotonin transporter) with alcohol dependence was small but significant (Feinn, Nellissery, & Kranzler, 2005; McHugh, Hofmann, Asnaani, Sawyer, & Otto, 2010). Later, research suggested *5-HTTLPR* to be tri-allelic (Hu et al., 2006), and the low-activity alleles (including the short and L_G alleles) have been thought to be associated with greater alcohol consumption as compared to the high-activity allele (including L_A allele).

Seven studies showed a significant moderating role of *5-HTTLPR* genotype in the associations of stressors with at least one drinking outcome. Specifically, two studies of early to late teenagers reported that, when exposed to family conflict or poor family relations, those carrying the short or low activity allele were more likely to drink and get intoxicated concurrently (Nilsson et al., 2005) and 6 months to three years later (Kim et al., 2015); among non-carriers, drinking behaviors did not differ depending upon the adverse family environment. Similar patterns of results were found in two studies of young adults. When exposed to a greater number of negative life events (e.g., breakup with a romantic partner, academic failure, losing a close friend, etc.) at ages 18 or 19, college students carrying the

short allele were more likely to engage in binge drinking one year later (Covault et al., 2007). Similarly, female (but not male) college students carrying the low activity allele were more likely to engage in binge drinking at age 20 when they experienced a greater number of stressors during the past year (Kranzler et al., 2012). Among non-carriers, these drinking behaviors did not differ depending upon the stressful environment. However, mixed or null findings were also found in the interaction between *5-HTTLPR* genotype and stressful environmental exposure. Specifically, the long or high activity allele (as opposed to short or low activity allele) was associated with a greater risk of binge drinking among individuals exposed to a number of stressful events at age 19 (Laucht et al., 2009) and individuals with poor adult attachment to parents at age 24 (Olsson et al., 2005). Finally, a large study (n = 1,913) found no differences in the association of stressful environments with alcoholism as a function of *5-HTTLPR* genotype (Dick et al., 2007).

Monoamine Oxidase A (MAO-A). The *MAO-A* number of tandem repeats (VNTR) is a gene that encodes a mitochondrial enzyme involved in the metabolism of dopamine, norepinephrine, and serotonin (Shih, Chen, & Ridd, 1999) and is located on X chromosome 11.3 (Levy et al., 1989). Compared to high activity alleles (i.e., 4 or 5-repeat alleles), the *MAO-A* low activity alleles (i.e., 2 or 3-repeat alleles) were found to reduce *MAO-A* transcriptional and enzyme expression activity, and have been associated with a greater risk for alcoholism (Contini, Marques, Garcia, Hutz, & Bau, 2006). Although sex differences regarding the risk conferring allele also have been reported (Herman et al., 2005; Meyer-Lindenberg et al., 2006), most studies have found that low activity alleles were positively associated with risk of alcoholism (Belsky & Beaver, 2011; Ducci et al., 2008; Stogner, 2015; Stogner & Gibson, 2013; Widom & Brzustowicz, 2006).

Two small prospective cGxE studies found that the *MAO-A* genotype moderated the effects of adverse family environments on young adult drinking, but with different risk

conferring alleles across sexes. One study of men (n = 66) found that, when exposed to both physical/emotional maltreatment and poor family relations, those carrying the low activity alleles were more likely to experience negative drinking consequences three years later (at ages 19 or 22; mean age was not reported) than non-carriers (Nilsson et al., 2007). Another study of women (n = 114) found that, when exposed to poor family relations, those carrying the high activity allele (as opposed to low activity alleles in men) experienced more negative drinking consequences and AUD symptoms than non-carriers (Nilsson, Wargelius, Sjoberg, Leppert, & Oreland, 2008).

Dopamine D4 receptor (DRD4). The *DRD4* gene is involved in modulating dopamine receptor function and cyclic adenosine monophosphate levels that affect sensitivity to feelings of reward. It is located on chromosome 11p15.5 and has a 48-basepair variable number of tandem repeats sequence ranging from 2- to 11- repeat alleles (Van Tol et al., 1992). Although evidence from behavioral studies on its association with drinking behavior is mixed, the long allele (7 or more repeat alleles found to reduce dopamine receptor function) has consistently been positively associated with drinking urge (for a review, see McGeary, 2009).

One study showed a significant moderating effect of *DRD4* genotype in the association of childhood adversity with alcohol dependence, but the finding was not replicated in another study. Specifically, when individuals had been physically and verbally abused in childhood, those with a *DRD4* long allele showed significantly more alcohol dependence symptoms across late adolescence and young adulthood (from ages 18 to 34); the association was not found among non-carriers (Park, Sher, Todorov, & Heath, 2011). However, in another study examining the 7-repeat allele as a risk allele (Carlson, Harden, Kretsch, Corbin, & Fromme, 2015), *DRD4* gneotype did not moderate the association of chilhood adversity with alcohol dependence at ages 18 to 26.

Dopamine D2 receptor (DRD2). The *DRD2* gene encodes the D2 type of the dopamine receptor (Grandy et al., 1989) and is located on chromosome 11q22-q23. Among diverse *DRD2* polymorphisms, the Taq1 (rs18004987) has been most commonly studied because of its relatively well-documented neurobiological functions. The Taq1A1 allele has been associated with reduced binding activity of the *DRD2* receptor (Thompson et al., 1997), which may be positively associated with reactivity to feelings of reward from alcohol use. A review and a meta-analysis indicated a significant but small association of the A1 allele with alcoholism after accounting for confounding factors (e.g., a lack of non-alcoholic control groups, Munafo, Matheson, & Flint, 2007; Noble, 2000).

The moderating role of *DRD2* genotype in the association of general life stressors with alcoholism has been reported among male adults with the mean age of 38 (Madrid, MacMurray, Lee, Anderson, & Comings, 2001). At higher levels of stressful life events, those carrying at least one A1 allele were more likely to endorse alcoholism symptoms on the Michigan Alcoholism Screening Test. However, the association was not shown among non-carriers.

Dopamine Transporter (DAT1). *DAT1* encodes the dopamine transporter, which plays a central role in modulating dopamine levels and is located on chromosome 5p15.3. Although some studies showed a significant association of *DAT1* 9-repeat or 10-repeat alleles with alcoholism and withdrawal symptoms (for a review, see Kohnke, 2008), other studies failed to find direct associations of *DAT1* with alcohol dependence (Bau et al., 2001; Choi et al., 2006).

Although the main effects of *DAT1* genotype on alcohol outcomes have been inconsistent, a recent cGxE study (n = 2,574, mean age = 15; Stogner, 2015) found a significant moderating effect of *DAT1* genotype in the association of stressful life events with lifetime alcohol use. At higher levels of stressful life events, adolescent females (but not

males) carrying the 10-repeat allele were more likely to consume alcohol than non-carriers.

Cumulative Genetic Score (CGS)

Although accumulating cGxE studies suggest differences in the degree of association between adverse, stressful environmental exposure and drinking behavior as a function of individual monoamine genes, the cumulative effect of multiple genetic variants rarely has been considered. A CGS approach has benefits in measuring and considering a number of genetic variants that may have demonstrated small effects in separate studies but that can co-exist in individuals to together influence their alcohol outcomes. Particularly, the effect of only a single genetic variant on complex behavior such as alcohol use and misuse is most likely small (Dick et al., 2015; Vink, 2016). Thus, examining the cumulative genetic score of multiple genetic variants is more likely to increase power and allows us to assess a more realistic and comprehensive genetic profile involved in drinking behaviors.

To my best knowledge, only one observational study has examined the interaction effects of a CGS involving *5-HTTLPR, DRD4, DAT1, DRD2*, and *MAO-A* genotypes with stressful environments on drinking behavior (Stogner & Gibson, 2016). When adolescents (*n* = 1,495, mean age = 15) were exposed to negative parental relationship, those who carried more risk genotypes initiated alcohol use at an earlier age compared to those who carried lower risk genotypes. However, cGxE studies using a cumulative genetic score approach with other genetic variants or on other outcomes are fast accumulating. For example, the effects of a family prevention program on adolescent alcohol use were found to differ as a function of adolescents' cumulative genetic score of *GABRG1*, *GABRA2*, and *DRD2* genotypes (Brody, Chen, & Beach, 2013). Also, the effects of a batterer intervention program on alcohol abstinence days and intimate partner violence were found to differ as a function of a cumulative genetic score of *5-HTTLPR* and *MAO-A* genotypes (Stuart, McGeary, Shorey, & Knopik, 2016). A cumulative genetic score approach also has been used within a cGxE

context to examine adolescent self-regulation (Belsky & Beaver, 2011), smoking abstinence rates (McGeary et al., 2012), reward sensitivity (Pearson, McGeary, & Beevers, 2014), and mood-congruent gaze bias (Disner, McGeary, Wells, Ellis, & Beevers, 2014). The potential value of this line of studies is the identification of a promising multi-locus genetic profile interacting with environmental factors to influence individuals' behaviors or traits.

Promise of Experimental Design in cGxE Studies

Although extant observational cGxE studies have contributed to an enhanced understanding of complex interactive effects between genetics and environments on drinking behavior, results of observational cGxE studies are possibly confounded by gene and environment correlation. Gene and environment correlation denotes that genes and environments are not independent, because individuals carrying certain genotypes may evoke or seek certain environments that are compatible with their genetic propensity (Plomin, DeFries, & Loehlin, 1977). For example, individuals carrying genotypes associated with vulnerability to stressor may increase their exposure to stressful environments by being easily angry at other people (i.e., evocative gene-environment correlation) or unconsciously/consciously selecting surroundings that cause stress (i.e., active gene-environment correlation). Thus, some observational cGxE studies may misrepresent gene-environment correlation as gene-environment interaction when gene-environment correlation are not appropriately accounted for. Thus, experimental study designs can better resolve these potential confounding effects of gene and environment correlation by assigning environmental conditions independent of a participant's genotype. No prior research with a cumulative genetic score has taken advantage of an experimental study design, although prior cGxE studies examining the effects of a single genetic variant on alcohol outcomes have used an experimental approach (Owens, Ray, & MacKillop, 2015; Ray, 2011).

Drinking Urge and Attentional Bias as Alcohol Endophenotypes

An endophenotype is a measurable component in the pathway from genotype to disorder (Gottesman & Gould, 2003). Endophenotypes have been found to have high sensitivity in screening for genes associated with alcohol dependence (Dick et al., 2006) and improving pharmacotherapy efficacy for alcoholism (Ray, Mackillop, & Monti, 2010). Thus, examining endophenotypes can greatly benefit cGxE studies by identifying genes associated with alcohol misuse that may be undetectable when examining phenotypes only. Two key alcohol endophenotypes worth examining are self-reported drinking urge and implicit attentional bias for alcohol related stimuli. Self-reported drinking urge has long been studied as an important alcohol endophenotype (for a review, see Sinha & O'Malley, 1999), particularly in association with relapse and treatment outcomes among alcohol dependent individuals (Bottlender & Soyka, 2004; Flannery, Poole, Gallop, & Volpicelli, 2003; Wapp, Burren, Znoj, & Moggi, 2015), although other studies showed mixed associations of drinking urge with alcohol use (MacKillop et al., 2010; Tiffany & Carter, 1998). There is also a considerable body of evidence for attentional bias for alcohol cues as an alcohol endophenotype among problem drinkers (Sharma, Albery, & Cook, 2001; Stormark, Laberg, Nordby, & Hugdahl, 2000; Townshend & Duka, 2001). Individuals who have alcohol problems have been found to perceive alcohol related stimuli as more salient and respond to alcohol stimuli faster than neutral stimuli. Electroencephalogram and event-related potentials studies provide neurobiological evidence for attentional bias by showing increased magnitude of substance cue activated brain regions (Vollstadt-Klein et al., 2012) and higher amplitudes of event-related potentials (Littel, Euser, Munafo, & Franken, 2012).

Mediation via Salivary Alpha-amylase Reactivity and Anxiety State

Potential biological and psychological mechanisms underlying the interactions between a cumulative genetic score of monoamine genes and stressful environmental exposure on alcohol outcomes need to be examined. The Sympathetic Adrenal Medullary

axis reactivity measured by salivary alpha-amylase level is a promising biological mediator of the monoamine genes and stressor interaction effects. Monoamine genes including serotonin genetic variants have been found to influence salivary alpha-amylase response in exposure to stressors (Frigerio et al., 2009; Mueller et al., 2012). For example, when infants had insecure attachment with parents, *5-HTTLPR* short allele carriers were found to have an elevated alpha-amylase response compared to non-carriers (Frigerio et al., 2009). Also, although the association of salivary alpha-amylase activity with alcohol behaviors has not been fully addressed yet, elevated salivary alpha amylase was associated with increases in other substance seeking behaviors (Duskova et al., 2010; Sinha et al., 2003).

In addition, anxiety state may serve as a psychological mediator of the monoamine genes and stressor interaction effects. The positive associations of anxiety with alcohol use disorder have been reported (for a review, see Zuckerman, 1999). Also, several studies have found significant associations of monoamine genes with anxiety state in response to stressors. For example, *5-HTTLPR* low activity allele carriers were found to experience more elevated anxious mood than non-carriers in response to daily life stressors (Brummett et al., 2008). Also, *MAO-A* low activity allele carriers were found to have more anxiety symptoms when they were exposed to family stressor, although the results were limited to boys (Lavigne et al., 2013).

Potential Confounding Factors

Demographic variables such as race and sex may confound the cGxE effects. Different racial groups have been found to have different allele or genotype frequencies (Hu et al., 2006), which may confound the results of genetic studies (called 'population stratification', Pritchard & Rosenberg, 1999; Yang, Zhao, Kranzler, & Gelernter, 2005). Also, the effects of stressors on alcohol cue reactivity have been found to differ depending on sex (Nesic & Duka, 2006). Previous studies involving monoamine genes also showed sex

differences in how individuals with those genes responded to adverse environments (Belsky & Beaver, 2011; Stogner & Gibson, 2016).

Goals of the Current Study

Using a within-subject experimental study design, this current study aimed to (a) examine whether a cumulative genetic score of *5-HTTLPR, DRD4, DAT1, DRD2*, and *MAO-A* genotypes moderates the effects of psychosocial stressors on drinking urge and attentional bias for alcohol related stimuli and (b) investigate the mediating roles of salivary alpha-amylase and anxiety state responses in the cGxE effects. It was hypothesized that the effects of stressors on drinking urge and attentional bias for alcohol would increase as individuals carry more risk conferring alleles of monoamine genes (i.e., their cumulative genetic score increases). It was also hypothesized that individuals with a higher cumulative genetic score would show higher levels of salivary alpha-amylase and anxiety in response to stressors, which in turn would be associated with elevated drinking urge and attentional bias for alcohol related stimuli.

Method

Participants

Participants were 105 Caucasian frequent binge drinkers (mean age = 19.83 [SD = 1.54]; 61% men) recruited from a mid-sized northeastern community. Only Caucasians were recruited to minimize confounding effects of population stratification. Frequent binge drinking was defined as drinking five or more alcoholic drinks for men and four or more alcoholic drinks for women on three or more occasions within the past two weeks, which has been used to screen for high-risk drinking among a young adult population (Knight et al., 2002).

Based on prior studies on stress response (de Rijk & de Kloet, 2014; Dickerson & Kemeny, 2004), exclusion criteria included (a) a blood alcohol content (BAC) level above

0.00% at session initiation, (b) use of a medication or current/ past medical or psychiatric diseases contraindicated with stress response (e.g., anti-depressants, hypertension medication, anti-psychosis medications), (c) current or history of alcohol dependence or treatment for alcohol related problems, and (d) smoking cigarettes every day or using psychoactive drugs that may compromise physiological measurements of stress response.

Participants were recruited using diverse methods, including the undergraduate research participation pool at a 4-year university in the community, flyers, classroom/email solicitations, and community online advertisements. Participants recruited from the undergraduate research participation pool were compensated with course credit. Participants recruited from other methods received monetary compensation of $35. All study procedures and measures were approved by university Institutional Review Board.

Procedures

Those who showed interest in participating in the study took part in a pre-screening assessment to ensure that they were eligible for the study before scheduling an experimental session. All experimental sessions were scheduled for late afternoon at 5pm and lasted until 8:30pm to approximate the time of natural drinking episodes. The eligible participants were informed that their BAC should be 0.00% at the pre-screening assessment, and their BAC was measured using a breathalyzer upon arriving at the laboratory. As shown in Figure 1, all participants went through a control condition first and then a stress condition.

The control condition period included baseline assessment, a control condition, in-vivo alcohol exposure, alcohol outcome measurement, and the first resting period. At baseline assessment, participants completed a questionnaire assessing demographics, alcohol use, stressful life events, and anxiety trait; they were also asked to donate their saliva for genotyping. At 10 minutes before the control condition began, participants were given a short scientific text and instructed to prepare to read it aloud for 10 minutes. In the control

condition, participants were asked to read the article for five minutes first and then to constantly count by fives (i.e., 5, 10, 15, 20…) and speak the series of the numbers for five minutes. The control condition was designed to be relatively simple and easy compared to the subsequent experimental stress condition (i.e., a public speaking task in front of a camera and constantly subtracted 13 starting from 2022, von Dawans, Kirschbaum, & Heinrichs, 2011). Before measuring participants' drinking urge and attentional bias, in-vivo alcohol cue exposure (Monti et al., 1987) was implemented. Participants were asked to hold a 1.5-oz cup of alcohol provided according to their alcohol preference (among beer, wine, and liquor) and smell it for 1 minute (but not to drink alcohol). In the resting period, participants were asked to watch a documentary film that did not include any potential stress-inducing or alcohol related stimuli for 40 minutes to allow their stress responses to decrease (Dickerson & Kemeny, 2004).

The stress condition period included a Trier Social Stress Test (Birkett, 2011), the same alcohol exposure and outcome measurement, the second resting period, and debriefing. At 10 minutes before the stress condition, a research assistant told participants that they would be given 10 minutes to prepare for a 5-minute speech about what they want to say in an interview for their dream job. In the stress condition, participants were instructed to give a speech in front of a video camera and two experimenters for five minutes. Experimenters did not give any verbal or non-verbal supportive feedback to the participants in order to increase evaluative stress (Dickerson & Kemeny, 2004). After the speech, participants were instructed to sequentially subtract the number 13 from 2022 and speak them for five minutes, which is designed to induce feelings of stress and uncontrollability. After the same alcohol cue exposure, participants' alcohol outcomes were assessed using the same measurements. Participants rested again for 40 minutes for their stress response to decrease, and finally were debriefed and compensated with research credit or monetary compensation.

Measures

Demographic information. Sex, age, and college student status were obtained through a self-report questionnaire.

Baseline alcohol use. To assess participants' alcohol use at baseline, Timeline Follow-Back (Sobell & Sobell, 1992) for the past 90 days and Alcohol Use Disorder Identification Test (Bohn, Krahn, & Staehler, 1995) were used. Frequency of binge drinking (defined as consuming four or more alcoholic drinks for women and five or more drinks for men) was calculated based on the Timeline Follow-Back. Frequency of binge drinking and a sum score of AUDIT items were used to examine baseline differences among cumulative genetic score groups and also used as covariates in sensitivity analyses.

Baseline stress levels. To assess participants' stress levels at baseline, a 36-item Life Events Scale for Students (Clements & Turpin, 1996) was used. Participants were asked about their experiences of stressors (e.g., death of a parent, major personal injury, academic and relationship problems, or illness) in the past year. Participants responded to whether the event happened last year (yes = 1; no =0) and also reported their subjective evaluation of the events based on a 5-point scale from -2 (*Extremely positive*) to 2 (*Extremely negative*). A sum score of the items that the participant endorsed as "*negative"* or *"extremely negative*" was used to examine baseline differences among three cumulative genetic score groups and also used as a covariate in sensitivity analyses.

Social desirability. Participants' tendency to produce socially desirable responses was measured using a 13-item Reynolds Short Form C of the Marlowe-Crown Social Desirability Scale (Reynolds, 1982). The scale showed high internal reliability (Fischer & Fick, 1993) and high test-retest reliability (Crino, Rubenfeld, & Willoughby, 1985). The items include "*It is sometimes hard for me to go on with my work if I am not encouraged*" and "*I have never deliberately said something that hurt someone's feelings"*. Participants

responded to each item with 0 (*False*) or 1 (*True*). The sum score (Cronbach's alpha = .67) was used to examine baseline differences among cumulative genetic score groups and also used as a covariate in a sensitivity analysis.

Genotypes and cumulative genetic risk score (CGS). All 105 participants' genotypes were analyzed except for two participants' *5-HTTLPR* and *MAO-A* genotypes that were not able to be genotyped due to low DNA concentration (2% indeterminate genotypes). Reliability of the genotypes was established by duplicate genotyping. The distribution of genotypes of *5-HTTLPR* was two short alleles (*n* = 13, 13%), one short and one long allele (*n* = 60, 58%), and two long alleles (*n* = 30, 29%). The distribution of genotypes of *DRD2* was two A1 alleles (*n* = 6, 6%), one A1 and one A2 allele (*n* = 32, 30%), and two A2 alleles (*n* =67, 64%). The distribution of genotypes of *DAT1* was two 10-repeat alleles (*n* = 53, 51%), one 10-repeat and one 9-repeat allele (*n* = 40, 38%), and two 9-repeat alleles (*n* =12, 11%). The distribution of genotypes of *MAO-A* was two low-activity alleles (*n* = 30, 29%), one low and one high activity allele (*n* = 20, 19%), and two high-activity alleles (*n* = 53, 52%). The distribution of genotypes of *DRD4* was two long alleles (*n* = 1, 1%), one short and one long allele (*n* = 28, 27%), and two short alleles (*n* = 76, 72%). Hardy-Weinberg equilibrium was investigated using Fisher's exact test (Wigginton, Cutler, & Abecasis, 2005). Allele frequencies of *5-HTTLPR, DAT1, MAO-A*, and *DRD2* were in Hardy-Weinberg equilibrium (*p*'s > 0.05). However, the Hardy-Weinberg equilibrium test could not be conducted for *DRD4* genotype, because a least five participants in each genotype category is required for running the test and there was only one participant with two *DRD4* long alleles.

CGS was generated by summing the number of alleles that have been associated with greater risk of alcohol misuse (Belsky & Beaver, 2011; Pearson et al., 2014; Stogner & Gibson, 2016). Based on previous candidate gene studies on alcohol outcomes, short allele of *5-HTTLPR*, long allele of *DRD4*, A1 allele of *DRD2*, 10-repeat allele of *DAT1*, and low

activity alleles of *MAO-A* were identified as risk conferring alleles. Regarding *5-HTTLPR* and *MAO-A* that had some conflicting findings on high risk alleles, risk alleles that have more neurobiological evidence (as described in Introduction section) were selected. Each polymorphism was assigned a point when at least one risk conferring allele was present, and then these values were added up to create CGS, potentially ranging from 0 (n = 0), 1 (n = 10), 2 (n = 35), 3 (n = 41), 4 (n = 16), to 5 (n = 3). Due to low frequencies in some allele categories, individuals with CGS of one or two were combined, and those with CGS of four or five were combined, resulting in three groups of low (n = 45; 43%), medium (n = 41; 39%), and high (n = 19; 18%) CGS scores. This re-categorization of cumulative genetic risk scores has been used in previous studies to increase power due to low allele frequencies (Belsky & Beaver, 2011; McGeary et al., 2012).

Alcohol Urge Questionnaire. Drinking urge was assessed after the control and stress conditions using the 8-item Alcohol Urge Questionnaire (Bohn et al., 1995). High internal consistency and test-retest reliability have been reported (Bohn et al., 1995; Drummond & Phillips, 2002), and high convergent validity with the Severity of Alcohol Dependence Questionnaire has been reported (Drummond & Phillips, 2002). The items include "*All I want to do now is have a drink*" and "*It would be difficult to turn down a drink this minute*". Participants responded to each item based on a 7-point response scale, with responses from 1 (*Strongly Disagree*) to 7 (*Strongly Agree*). For the current analyses, the sum scores of the eight items after the control (Cronbach's alpha = .91) and stress (Cronbach's alpha = .93) conditions were used as dependent variables.

Visual Probe Task. The Visual Probe Task is a well-established protocol to investigate participants' attentional bias towards a substance related stimuli (Ehrman et al., 2002). Studies have suggested that people with increased urge to drink have a shorter reaction time in replacing alcohol-related images (Field & Cox, 2008; Field & Powell, 2007). Pairs of

alcohol-related pictures (e.g., glass of beer) and neutral pictures (e.g., a chair) were shown. Simple alcohol pictures were used because they were found to be more effective at capturing drinker's attention than complex alcohol images (Miller & Fillmore, 2010). Fixation point (x) was shown for 500 ms in the center, followed by a pair of alcohol-related and neutral pictures in which one is shown on the left side and another shown on the right side for 1000 ms. When pictures disappeared from the screen, the fixation point (x) appeared on the left or right side, and participants were asked to answer which picture was located on that side. Participants were given two blocks of 84 trials. For the current analyses, their reaction time ratios of alcohol-related pictures to neutral pictures after control and stress conditions were used as dependent variables.

Manipulation check of stress induction. Anxiety state, heart rate, and salivary alpha-amylase response have been frequently used as manipulation checks of stress induction in previous studies (Birkett, 2011; Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009; von Dawans et al., 2011).

Anxiety state. Anxiety state was assessed using the 20-item state anxiety scale of the State-Trait Anxiety Inventory Form Y (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Participants reported how intensely they feel tense, upset, or frightened at that moment based on a 4-point response scale, including 0 (*Not at all*) to 3 (*Very much so*). This scale has been shown to be highly reliable (Spielberger, 1989), and it has shown high convergent validity with the Beck Anxiety Inventory (Balsamo et al., 2013). Anxiety states measured five times across control and stress conditions and after the final resting period (Cronbach's alpha = .87 to .95) were analyzed to check stress manipulation.

Heart rate. Heart rate was measured for 30 minutes each in the control and stress conditions. It was measured using a chest strap Polar H7 bluetooth heart rate monitor (Polar Electro Oy, Kempele, Finland). The Polar H7 heart rate monitor has been found to have a

good concurrent validity with a pulse oximeter (Cheatham, Kolber, & Ernst, 2015). Mean scores of heart rate each five minutes (six times each in control and stress conditions) during control and stress conditions were analyzed.

Salivary alpha-amylase. Salivary alpha-amylase was assessed by the Salivette device (Sarstedt, Newton, NC). Participants were asked to put a cotton swab in their mouth and chew it gently for two minutes until it is completely saturated with saliva. The analysis of salivary alpha-amylase was completed using an enzyme kinetic method shown to be reliable and valid (Bosch et al., 2003; Rohleder & Nater, 2009). Amylase levels measured five times across control and stress conditions and after the final resting period were analyzed to check stress manipulation.

Mediator measures. The anxiety state and salivary alpha-amylase levels mentioned above were also used as potential mediator variables. In order to examine their mediating roles in interaction effect between CGS and psychosocial stressor on drinking urge, change scores of anxiety states and salivary alpha-amylase between control and stress conditions were used.

Data Analyses

Descriptive analyses. Sample characteristics and baseline differences as a function of CGS levels were analyzed using *SPSS* Version 24.0 (IBM, 2016).

Manipulation checks. The effect of the stress manipulation on anxiety state, heart rate, and salivary alpha-amylase was examined using a repeated measures ANOVA using *SPSS*.

Interactions between CGS and stressor. In order to examine the interaction effect of CGS and psychosocial stressor on drinking urge, two-way mixed analyses of variance (ANOVA) was conducted in *SPSS*. A two-way mixed ANOVA was conducted to examine a mixture effect of a between-subject factor (i.e., CGS) and a within-subject factor (i.e.,

experimental condition). Two sets of mixed ANOVA models were estimated to examine the cGxE effects on the two alcohol outcomes of drinking urge and attentional bias for alcohol. The main effect of CGS (cG), main effect of experimental stress versus control conditions (E), and interaction effect of the grand-mean centered CGS with experimental conditions (cGxE) were examined on drinking urge and the visual probe task score in separate models. The confounding effect of sex was controlled for in all analyses by including it as a covariate. If a significant cGxE effect were found, a post-hoc paired samples t-test was separately conducted depending on cumulative genetic score.

The assumptions of ANOVA were checked before conducing any analyses. First, regarding the normality of residuals assumption, the interquartile range (IQR) was calculated by subtracting the first quartile (Q1) from the third quartile (Q3), and outliers below Q1-1.5 x IQR and above Q3 + 1.5 x IQR were dropped (Vogt & Johnson, 2011). Outliers on the Visual Probe Task outcomes in the control (n = 4) and stress (n = 1) conditions were dropped. Then, Shapiro-Wilk normality testing (Razali & Wah, 2011) for outcome residuals was conducted: the residuals of Visual Probe Task outcomes were normally distributed (S-W = .99, df = 101, p = .85−.88), but residuals of the Alcohol Urge Questionnaire were not normally distributed (S-W = .96−.97, df = 104, p = .01−.03). Thus, Alcohol Urge Questionnaire responses were transformed to a normal distribution using a rank transformation method described in a previous study (Solomon & Sawilowsky, 2009). All alcohol outcomes met the assumption of equality of error variances. Sphericity (i.e., variances of independent variable levels should be equal in case that there are three or more levels; Girden, 1992), was not required, because there were only two time points when alcohol outcomes were measured (i.e., stress versus control conditions). Other assumptions were automatically met based on the current study design (i.e., the dependent variables were continuous, the same group of participants were exposed to both control and stress conditions).

Mediating effects of anxiety state and salivary alpha-amylase. Two models were estimated to separately examine potential mediators: changes in salivary alpha-amylase and anxiety state between control and stress conditions. The *SPSS* macro PROCESS was used to test for significant mediated moderation (Hayes, 2013). Estimates of mediated effects and their 95% confidence intervals were obtained by bootstrap analysis with 5,000 bootstrap samples. The 95% confidence interval (CI) of the mediated effect that does not include zero indicates a significant mediation effect.

Prior power analysis. To determine the appropriate sample size to detect true gene and environment interaction effects, a power analysis was performed using the Quanto program version 1.2.4. (Gauderman & Morrison, 2009) under the conditions of a dominant genetic model and continuous environmental and alcohol outcome measures. Expected effect sizes (R^2) of the interaction between a monoamine genotype (i.e., *5-HTTLPR*) and stressful environments on alcohol outcomes (R^2 = 0.065; Kim et al., 2015), the main effect of the monoamine genotype on alcohol outcomes (R^2 = 0.023; Covault et al., 2007), and the main effect of stressful environments on alcohol outcomes (R^2 = 0.069; Park, Armeli, & Tennen, 2004) were based on prior studies. The result of power analysis showed that the necessary sample size that reaches power of 0.80 for a between-subjects study is 106. For the current within-subjects study, the sample size of 106 is assumed to have a higher power than 0.80 due to lower sample variability than a between-subjects study.

Results

Descriptive Statistics

All participants were college students (3% part-time, 97% full-time students), although participant eligibility criteria did not restrict to college students. As presented in Table 1, participants' average score on the Alcohol Use Disorder Identification Test was 12.89 (*SD* = 4.45), which is in a risky or hazardous alcohol use range. There were no baseline

differences on sociodemographic, stressful life events, and alcohol variables as a function of CGS except for social desirability, $F(2,102) = 4.22$, $p = 0.02$, $n_p^2 = .08$. Tukey's HSD indicated that participants with 4 or 5 risk alleles showed a higher social desirability than those with 1 or 2 risk alleles, $p = 0.04$. Thus, sensitivity analysis was conducted after controlling for the effect of social desirability on self-reported drinking urge as described below.

Bivariate correlation coefficients of study variables are presented in Table 2. Alcohol Use Disorder Identification Test score was positively associated with binge drinking frequency in the past 90 days, $r = .55$, $p < .001$. Social desirability was positively associated with cumulative genetic score, $r = .27$, $p = .01$, and with alcohol urge questionnaire response after the control condition, $r = .22$, $p = .03$. Alcohol urge questionnaire responses after control and stress conditions were positively correlated with each other, $r = .54–.86$, $p < .001$, but visual probe task scores measured after control and stress conditions were not significantly correlated to each other, $r = -.07$, $p = .46$.

Stress Manipulation Check

Changes of anxiety state, salivary alpha-amylase, and heart rate responses in control and stress conditions are presented in Figure 2. The effect of the stress manipulation on these three stress response measures was examined using a repeated measures ANOVA, and overall results showed that stress was successfully manipulated. Regarding anxiety state, a significant effect of experimental conditions was found, $F(1,98) = 28.93$, $p < .001$. A post-hoc paired samples t-test indicated that anxiety level measured right after the stress condition was significantly higher than right after the control condition, $t(100) = 7.67$, $p < .001$. The same pattern was found in salivary alpha-amylase, $F(1,92) = 33.84$, $p < .001$, and heart rate, $F(1,89) = 6.03$, $p = .02$. The amylase level measured right after the stress condition was significantly higher than right after the control condition, $t(96) = 7.19$, $p < .001$. Also, two

heart rates (i.e., mean values of five minutes each) measured in the stress condition were significantly higher than in the control condition, $t(96) = 5.80-9.78$, p's < .001. Additionally, on a manipulation check questionnaire that was administered before debriefing, 79% of participants endorsed that they were concerned/nervous in a stress condition, whereas only 8% of participants endorsed that they were concerned/nervous in a control condition.

CGS and Experimental Condition Interaction Effect

Results of mixed ANOVA to test CGS and experimental condition interaction effect on alcohol outcomes are presented in Table 3. For the Alcohol Urge Questionnaire outcome, analysis demonstrated no significant interaction effects of CGS with experimental condition in predicting self-reported drinking urge, $F(2,99) = 0.42$, $p = .66$, $n_p^2 = .00$, after controlling for sex. However, the result showed a significant main effect of CGS on the Alcohol Urge Questionnaire outcome, $F(2,99) = 3.76$, $p = .03$, $n_p^2 = .07$. Post-hoc pairwise comparisons of estimated marginal means (adjusted for sex) demonstrated that participants with four or five risk alleles reported a higher drinking urge than those with three risk alleles, $p < .001$, or those with one or two risk alleles, $p = .02$ (independent of experimental condition). Participants went through both the control and stress conditions in order, and their Alcohol Urge Questionnaire outcomes did not significantly change depending on the experimental conditions, $F(1,100) = 0.41$, $p = .52$, $n_p^2 = .004$.

For the Visual Probe Task outcome, mixed ANOVA demonstrated a significant interaction effect of CGS with experimental condition in predicting attentional bias towards alcohol pictures, $F(2,97) = 4.44$, $p = .01$, $n_p^2 = .08$, after controlling for sex. The significant interaction pattern between the number of risk conferring alleles (i.e., three groups of CGS scores) and experimental conditions on predicted values of visual probe task scores are presented in Figure 3. Post-hoc paired samples t-test of the predicted values showed that individuals carrying four or five risk conferring alleles showed a significantly higher visual

probe task score in the stress condition compared to the control condition, $t(17) = 38.29$, $p < .001$. Individuals carrying three risk conferring alleles also showed a significantly higher visual probe task score in the stress condition compared to the control condition, $t(38) = 11.90$, $p < .001$. On the contrary, individuals carrying one or two risk conferring alleles showed a significantly lower visual probe task score in a stress condition than a control condition, $t(43) = -51.70$, $p < .001$.

Mediating Roles of Alpha-amylase and Anxiety State

Results of mediation analyses to test mediating roles of alpha-amylase and anxiety in the significant interaction effect of CGS and experimental condition on Visual Probe Task outcome are presented in Figure 4. No significant mediation effect of alpha-amylase was indicated, $b = -0.34$, $\beta = -.01$, 95% bootstrapped CI [-3.23, 0.45], $SE = 0.73$, $p = .60$. Specifically, the indirect path from CGS to the alpha-amylase change between control and stress conditions (b = -6.19, $\beta = -.13$, $p = .21$), as well as the indirect path from alpha-amylase to Visual Probe Task change between control and stress conditions (b = 0.05, $\beta = .07$, $p = .48$), were not significant after controlling for sex. However, the direct effect of CGS on Visual Probe Task change was significant, b = 11.02, $\beta = .32$, $p = .003$, after accounting for the indirect and sex effects.

No significant mediation effect of anxiety state was indicated, $b = -0.70$, $\beta = -.02$, 95% bootstrapped CI [-2.67, 0.08], $SE = 0.64$, $p = .39$. Specifically, the indirect path from CGS to anxiety state change between control and stress conditions (b = -1.72, $\beta = -.16$, $p = .12$), as well as the indirect path from anxiety state to Visual Probe Task change between control and stress conditions (b = 0.41, $\beta = .12$, $p = .20$), were not significant after controlling for sex. However, the direct path of CGS on Visual Probe Task change was significant, b = 10.84, $\beta = .31$, $p = .002$, after accounting for the indirect and sex effects.

Sensitivity Analyses

Two sets of analyses were conducted to examine whether the cGxE interaction results were robust. First, all analyses were conducted controlling for the effects of baseline variables including Alcohol Use Disorder Identification Test, binge drinking frequency, and life stress events in addition to sex. Significant cGxE effect on Visual Probe Task remained the same, $F(2,93) = 6.53$, $p = .02$, $n_p^2 = .08$, and non-significant cGxE effects on Alcohol Urge Questionnaire remained the same, $F(2,95) = .36$, $p = .69$, $n_p^2 = .01$. Second, analysis of the Alcohol Urge Questionnaire outcome was conducted while controlling for the effects of social desirability. When controlling for social desirability in addition to sex, the non-significant cGxE effect on Alcohol Urge Questionnaire remained the same, $F(2,98) = 0.38$, $p = .69$, $n_p^2 = .01$.

Discussion

The current study extended cGxE literature on alcohol phenotypes by examining the interaction effects of a cumulative genetic score of five monoamine genotypes (*5-HTTLPR*, *MAOA-A*, *DRD4*, *DAT1*, and *DRD2*) with psychosocial stressors on two alcohol endophenotypes among frequent heavy drinkers. This study also extended previous observational cGxE studies examining chronic stressors by examining the effect of experimentally manipulated acute stressors in cGxE context. Regarding attentional bias, a greater level of cumulative genetic score was positively associated with faster reaction to alcohol related stimuli in the stress condition but not in the control condition. Regarding drinking urge, a greater level of cumulative genetic score was positively associated with drinking urge in both stress and control conditions. These findings suggest that the effect of risk-conferring alleles of the five monoamine genes on attentional bias for alcohol stimuli may differ depending on exposure to stressful environments, but drinking urge may be mainly influenced by monoamine genetic effect regardless of stressful environmental exposures.

Our finding of attentional bias toward alcohol stimuli showed a cross-over interaction in that the cumulative genetic score is associated with greater attentional bias for alcohol stimuli in the stress condition but lower attentional bias for alcohol stimuli in the control condition. These cross-over patterns were observed in two previous large cGxE studies (n = 1,495, Stogner & Gibson, 2016; n = 1,586, Belsky & Beaver, 2011) on cumulative effects of the same five monoamine genes examined in the current study. Specifically, when adolescents experienced high levels of family relationship stressors, those with a higher cumulative genetic score were more likely to initiate alcohol use at an earlier age (Stogner & Gibson, 2016); when adolescents experienced low levels of family relationship stressor or no stressor, those with a higher cumulative genetic score initiated alcohol use at a later age. Although not an alcohol outcome, it was also found that, when adolescents experienced poor parenting, those with a high cumulative genetic score showed significantly poorer self-regulation (Belsky & Beaver, 2011). On the contrary, when adolescents experienced good parenting, those with a high cumulative genetic score showed significantly better self-regulation than those with a lower cumulative genetic score. This cross-over pattern of interaction supports a differential susceptibility hypothesis rather than diathesis stress model. That is, the current study findings indicate that the five monoamine genes may be 'plasticity genes' that are associated with sensitivity to both positive and negative environmental exposures rather than 'risky genes' as pathogens of alcohol misuse. Individuals with a high CGS with the five monoamine genes may be genetically plastic individuals (rather than genetically vulnerable individuals) who show worse outcomes in adverse environments but better outcomes in protective environments than non-plastic individuals. However, cross-over patterns of interaction may be an artifact due to a low power and small sample size (Boardman et al., 2014; Sher & Steinley, 2013), and thus the current study findings await replication in large, independent samples.

This study did not find significant mediating roles of anxiety state or Sympathetic Adrenal Medullary axis reaction measured by salivary alpha-amylase in the interaction effects of cumulative genetic score with psychosocial stressor on attentional bias for alcohol stimuli. The non-significant mediating role of anxiety state is surprising given considerable evidence of co-occurring problematic alcohol use and internalizing symptoms (especially depression and anxiety) among monoamine plasticity genotype carriers (for a review, see Saraceno, Munafo, Heron, Craddock, & van den Bree, 2009). One possible explanation for the non-significant mediation is that self-reported anxiety state may not capture automatic and unconscious negative reactions to stressful environment among monoamine plasticity genotype carriers. The automatic negative responses among monoamine plasticity genotype carriers have been captured through a measure such as selective attention to negative stimuli. A meta-analysis of ten published studies (Pergamin-Hight, Bakermans-Kranenburg, van Ijzendoorn, & Bar-Haim, 2012) reported that individuals with *5-HTTLPR* low activity allele showed elevated selective attention to negative stimuli compared to non-carriers. More importantly, a recent cGxE study involving a CGS of three serotonin genes reported that, when sad mood was induced in an experimental setting, individuals with a higher CGS showed a more elevated attentional bias for negative stimuli (Disner et al., 2014). Thus, monoamine genetic variants may be positively associated with selective attention to negative stimuli, which in turn is positively associated with attentional bias for alcohol cues in stressful environments. Sympathetic Adrenal Medullary axis reactivity measured by salivary alpha-amylase, which showed significant associations with monoamine genotypes in previous studies (Frigerio et al., 2009; Mueller et al., 2012), also did not show a significant mediating role. One possible explanation for this non-significant mediation is that, although salivary alpha-amylase is widely accepted as a physical stress measure (Het et al., 2009; Maruyama et al., 2012; Nater et al., 2006), there is also a concern that amylase is reflective of sympathetic

nervous system response, which has a broader set of activating stimuli. Amylase is known to be a little more active than hypothalamic-pituitary-adrenal axis response measured by cortisol, which needs strong social evaluative stress to be activated (Buss, Davidson, Kalin, & Goldsmith, 2004; Lundberg & Frankenhaeuser, 1980). Thus, it is plausible that amylase may have been confounded due to other non-stress related stimuli during experiment. Cortisol levels are known to generally peak at 10-15 minutes after stress exposure (Het et al., 2009) as opposed to salivary alpha-amylase that shows an immediate response after stressors (Maruyama et al., 2012). Cortisol response was not analyzed in this current study because saliva samples in this current study were collected right after a stress condition. Therefore, future studies need to examine a potential mediating role of cortisol levels about 10 to 15 minutes after stress exposure.

Different from attentional bias, the cumulative genetic effect of five monoamine genotypes on drinking urge did not differ as a function of manipulated psychosocial stressors. Rather, a greater level of cumulative genetic score was positively associated with drinking urge regardless of control versus stress conditions. Monoamine (particularly dopaminergic) neurotransmission has long been suggested as a neuropathway for substance craving (for a review, see Berridge & Robinson, 1998). This finding is also in line with the prior association studies' finding regarding main effects of monoamine genotypes on drinking urge. For example, *DRD4* long or 7 allele alleles have been positively associated with drinking urge (Hutchison, McGeary, Smolen, Bryan, & Swift, 2002; Hutchison et al., 2003), and several polymorphisms of *DRD2* and *DAT* genes have been also associated with elevated drinking urge in a genome wide study (Agrawal et al., 2013). However, the lack of moderating effect of experimentally manipulated psychosocial stressor on drinking urge was unexpected and incongruent with the significant moderating role of stressor in attentional bias for alcohol cues. This discrepant finding in self-reported drinking urge versus implicit measure of

drinking urge (i.e., attentional bias for alcohol stimuli) might be in part due to a confounding effect of a high social desirability on drinking urge. As reported in the Descriptive Statistics section above, a high cumulative genetic score group was found to have a significantly higher social desirability than lower cumulative genetic score groups. Thus, a high cumulative genetic score group may have reported an elevated drinking urge across control and stress conditions because they believed that it will be viewed more favorably by researchers. However, social desirability may have not affected their attentional bias score, which is a more automatic and unconscious response. Indeed, the discrepancy between attentional bias and drinking urge has been reported in several studies. A meta-analysis reported that the correlation between attentional bias and subjective craving in substance use is significant but small (r = .19) and shared variance between the two is less than 4% (Field, Munafo, & Franken, 2009). Self-reported drinking urge and implicit attentional bias of one's motivational state toward drinking may operate relatively independently (Ryan, 2002), although the two may also reciprocally affect each other. The small correlation between the two is partly because self-reported drinking urge requires individuals' conscious appraisal of their physical or emotional urge to drink, whereas attentional processing typically occurs automatically in an unconscious state (Tiffany & Conklin, 2000).

These study findings have potential clinical implications for prevention and intervention efforts to curtail alcohol misuse among young adults. cGxE findings in general allow us to identify the "high-risk" group based on genotypes that are more vulnerable to certain environmental effects. Although individuals' genotypes cannot be changed, cGxE findings can help us to design targeted prevention or intervention strategies for a population at risk of drinking problems. Useful strategies may include intervening to reduce the potential detrimental effects of the environmental exposure. The current finding informs us that stressful environments should be addressed in alcohol intervention or prevention programs

for young adults with a high cumulative genetic score. Of particular interest, a previous study demonstrated that, among men with a high cumulative genetic score of *5-HTTLPR* and *MAOA-A* genotypes, those who received an intimate partner violence treatment and alcohol intervention showed significantly more abstinent days and less physical violence perpetration compared to those who did not receive the intervention (Stuart et al., 2016). This finding highlights the promise of genetically informed intervention efforts to reduce the risk of drinking. In addition, attentional bias modification training (which is designed to train individuals to disengage attention from alcohol related stimuli) has been found to be effective in reducing alcohol misuse (Fadardi & Cox, 2009) and maintaining a longer abstinence period (Schoenmakers et al., 2010). Given the current study's finding regarding attentional bias, individuals with a high cumulative genetic score of five monoamine genes who are also exposed to stressful environments may benefit from the attentional bias modification training.

Findings of the current study should be interpreted within the context of several limitations. First, although the genotypes included in this study are selected based on previous cGxE study findings, the selected monoamine genes would not be the only risk conferring genes for alcohol endophenotypes. Thus, genome-wide GxE studies using atheoretical genetic variant finding approach need to determine whether these five monoamine genes remain significantly associated with alcohol outcomes in the context of other genes in stressful environments. No association of monoamine genes examined in the current study with alcoholism was found in genome wide association studies (Edenberg et al., 2010; Gelernter et al., 2014; Wang et al., 2013). Extant genome wide GxE interaction studies on alcoholism (Polimanti et al., 2017; Salvatore et al., 2014) have not tested the five monoamine genetic effects. Second, we did not examine gene-gene-environment interactions due to our small sample size and low statistical power for three-way interaction effects. The cumulative genetic effect observed in the current study may be the result of one genetic

variant strengthening another variant's effect in stressful environments. For example, *MAO-A* low activity allele was found to be 3.48 times more positively associated with alcohol dependence in people carrying *DRD2* A1A1 genotype (Huang et al., 2007). However, the possible gene-gene-environment interaction pairs with five different genes are numerous, and thus exploring the three-way interactions require a much larger sample size. Third, our cumulative genetic approach assumes equal contribution of each individual gene into the cumulative genetic effect. However, each monoamine gene's contribution to alcohol endophenotypes may significantly differ from each other, although evidence for differences in effect sizes of the five monoamine genotypes is insufficient in the current literature. This weighted cumulative score approach where the weights are assigned to each variant based on its reported effect in genome wide association studies has been used in recent studies on alcohol outcomes (Diószegi et al., 2017; Vink et al., 2014). As more evidence of five monoamine genotypes accumulates, future studies may use a weighted cumulative genetic score in GxE context. Fourth, there is a possibility that our small sample size may have resulted in false positives or negatives. Particularly, there has been a concern about a high potential of false positives in cGxE studies with small samples (Hewitt, 2012), because there are various environments with different definitions and measurements. Also, because it is statistically more difficult to detect cGxE interaction effects compared to main effects (McClelland & Judd, 1993), there may be a high potential of false negatives due to small sample size. Thus, the current findings need to be replicated across independent and large samples. Finally, potential limitations in external validity arise from the nature of this study's experimental design manipulating stressor in a controlled situation. The observed relationships in a controlled setting may not be generalized into everyday situations where other factors are also affecting the relationships. Also, in order to exclude potential confounding factors on stress response, young adults who were regularly using psychoactive

drugs were excluded at prescreening. For ethical reasons, individuals who have ever received treatment for alcohol-related problems were excluded from this study where alcohol cues are repeatedly presented. Thus, this current finding may not be generalized to binge drinkers who are also regular drug users and alcohol treatment seeking young adults.

Despite these potential limitations in external validity, the benefits of experimental study design are particularly important in cGxE research on alcohol outcomes. An experimental design allows us to measure endophenotypes that have high sensitivity in screening genes associated with alcohol dependence and control for confounding effect of gene-environment correlation, which has been a concern in observational studies. Therefore, the current study advances the existing cGxE literature by using a cumulative genetic score approach in an experimental setting and contributes to a better understanding of the complex and multi-faceted etiologies of alcohol misuse among young adults.

Table 1

Descriptive Statistics of All Participants and Baseline Differences as a Function of the CGS

Variable (possible range)	1 or 2 risk alleles Low CGS (n = 45)	3 risk alleles Medium CGS (n = 41)	4 or 5 risk alleles High CGS (n =19)	Test statistics comparing Low vs Medium vs High CGS
Male sex	64 %	61 %	53 %	$\chi^2(2) = 0.78$
Stressful life events in the last year (0–36)	3.04 [2.26]	2.68 [2.14]	2.74 [2.23]	$F(2,101) = 0.33$
Social desirability (0–33)	15.06 [4.69]	17.22 [4.23]	18.00 [3.37]	$F(2,102) = 4.22$*
Alcohol baseline measure				
AUDIT (0-40)	12.96 [4.71]	13.32 [4.56]	11.79 [3.51]	$F(2,102) = 0.77$
Binge drinking frequency (0-90)	20.42 [11.00]	19.90 [10.48]	15.79 [8.13]	$F(2,101) = 1.43$

Note. CGS = Cumulative Genetic Risk Score, AUDIT = Alcohol Use Disorder Identification Test, AUQ = Alcohol Urge Questionnaire.

* $p < .05$

Table 2

Means (and Standard Deviations) or Percentages and Bivariate Correlation Coefficients of Study Variables

Variable (possible range)	*M* (*SD*)	1	2	3	4	5	6	7	8	9
1. Male sex	61%	—								
2. Cumulative Genetic Score (0–2)	0.75 (0.74)	-.08	—							
3. Stressful life events (0–36)	2.85 (2.19)	.15	-.07	—						
4. Social desirability (0–33)	16.44 (4.43)	-.09	.27**	-.08	—					
5. AUDIT (0–40)	12.89 (4.45)	.03	-.07	.18	-.05	—				
6.Binge drinking frequency (0–90)	19.38 (10.38)	.05	-.14	-.03	-.06	.55**	—			
7. AUQ – control condition (1–7)	3.41 (1.60)	-.13	.19*	-.19	.22*	.12	.02	—		
8. AUQ – stress condition (1–7)	3.44 (1.67)	-.16	.15	-.13	.15	.14	.05	.82**	—	
9. VPT – control condition	1.00 (17.13)	-.02	-.23*	-.05	-.14	.18	.06	-.11	-.04	—
10. VPT – stress condition	-0.39 (18.43)	.07	.13	-.03	-.003	.06	.003	.04	-.01	-.07

Note. AUDIT = Alcohol Use Disorder Identification Test, AUQ = Alcohol Urge Question, VPT = Visual Probe Task. For correlation coefficient of sex, Spearman correlation coefficients are presented; for other variables, Pearson correlation coefficients are presented. *$p < .05$, **$p < .01$

Table 3

Observed Means (and Standard Deviations) of Alcohol Outcomes by CGS and Experimental Condition, and Mixed ANOVA Analyses Examining the Interaction Effect of CGS and Experimental Condition on Alcohol Outcomes

Variables	Low CGS group	Middle CGS group	High CGS group	Main effect of CGS		Main effect of Experimental condition		CGS x condition Interaction effect	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*F* statistics	n_p^2	*F* statistics	n_p^2	*F* statistics	n_p^2
Drinking urge									
AUQ									
Control condition	3.25 (1.47)	3.19 (1.54)	4.26 (1.39)	F(2,99) =3.76*	0.07	F(1,99) =0.40	0.004	F(2,99) =0.42	<.001
Stress condition	3.40 (1.74)	3.14 (1.51)	4.32 (1.46)						
Attentional bias									
VPT[a]									
Control condition	5.19 (17.71)	-1.07 (15.24)	-4.73 (18.00)	F(2,97) =0.05	0.001	F(1,97) =0.00	<.001	F(2,97) =4.44*	0.08
Stress condition	-3.55 (14.80)	1.09 (18.68)	5.91 (22.24)						

Note. CGS = Cumulative Genetic Risk Score, AUQ = Alcohol Urge Questionnaire outcome, VPT = Visual Probe Task score, [a] = a rank-based normal transformation was applied; sex was included as a covariate in all analyses

*$p < .05$

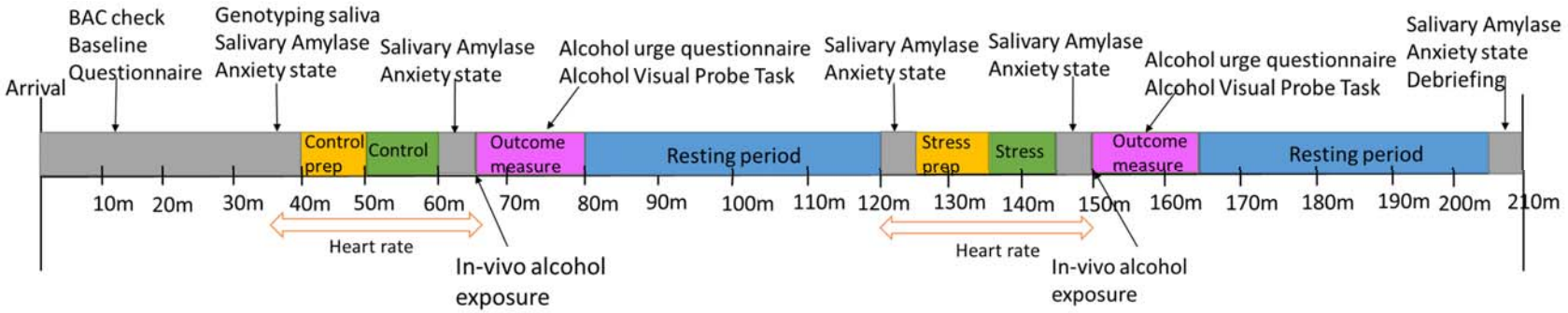

Figure 1. Experimental protocol. BAC = blood alcohol content; m = minutes; Control prep = a control condition preparation period; Control = a control condition; Stress prep = an experimental stress condition preparation period; Stress = a stress condition.

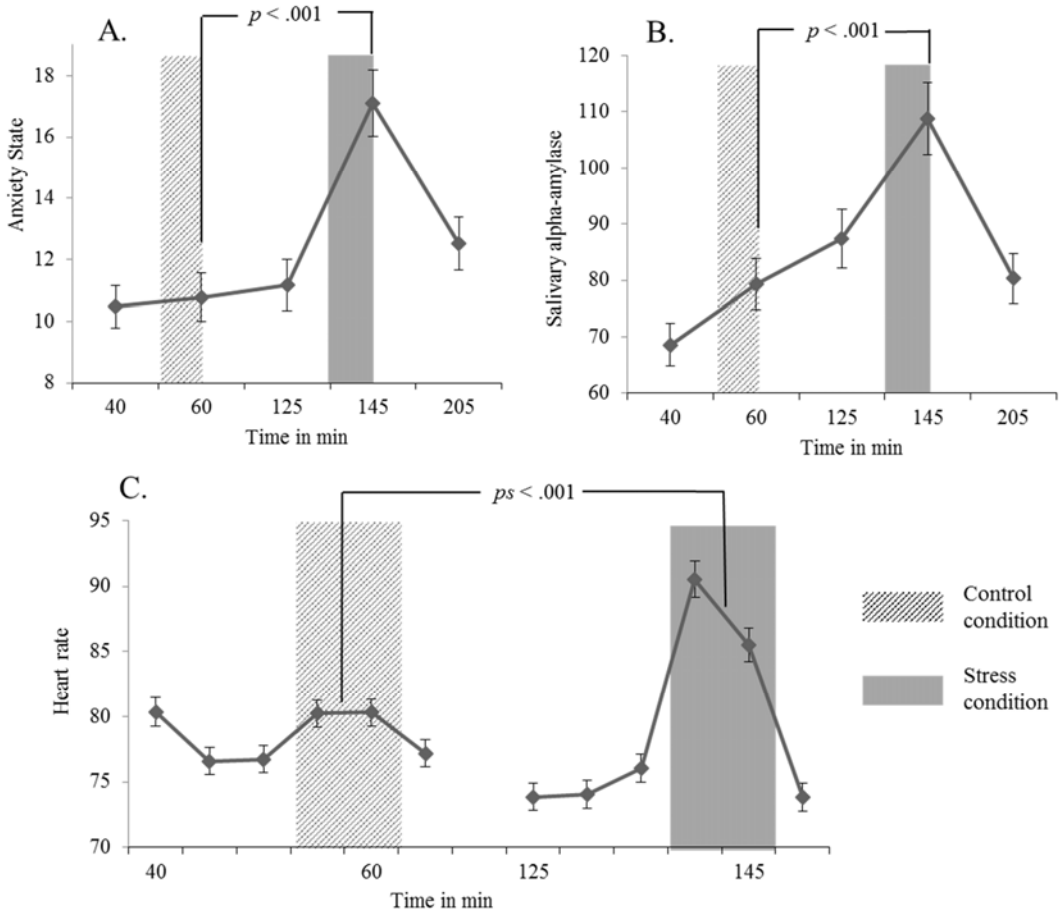

Figure 2. Observed mean levels (and standard error bars) of anxiety state, salivary alpha-amylase, and heart rate responses throughout the experimental procedures.

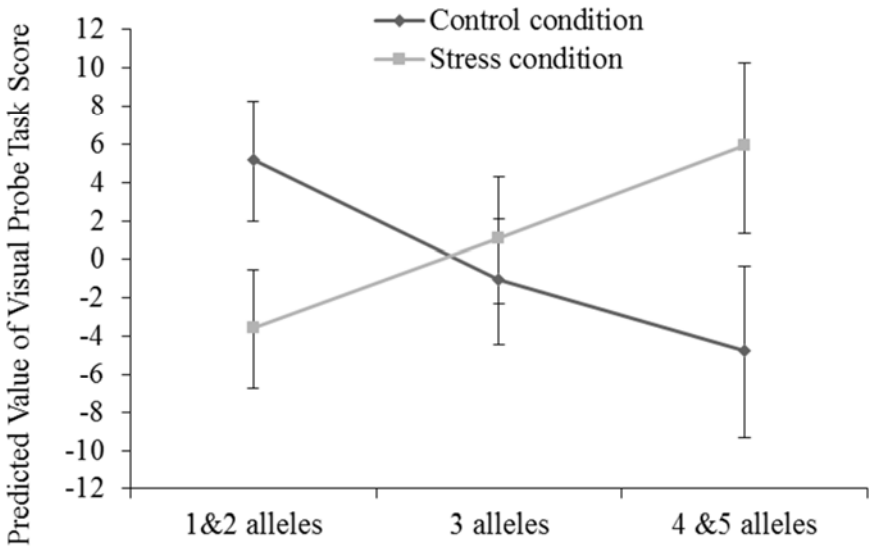

Figure 3. Predicted means (and standard error bars) of visual probe task scores among carriers of low (1 or 2 risk alleles), middle (3 risk alleles) and high (4 or 5 alleles) cumulative genetic groups in control and stress experimental conditions.

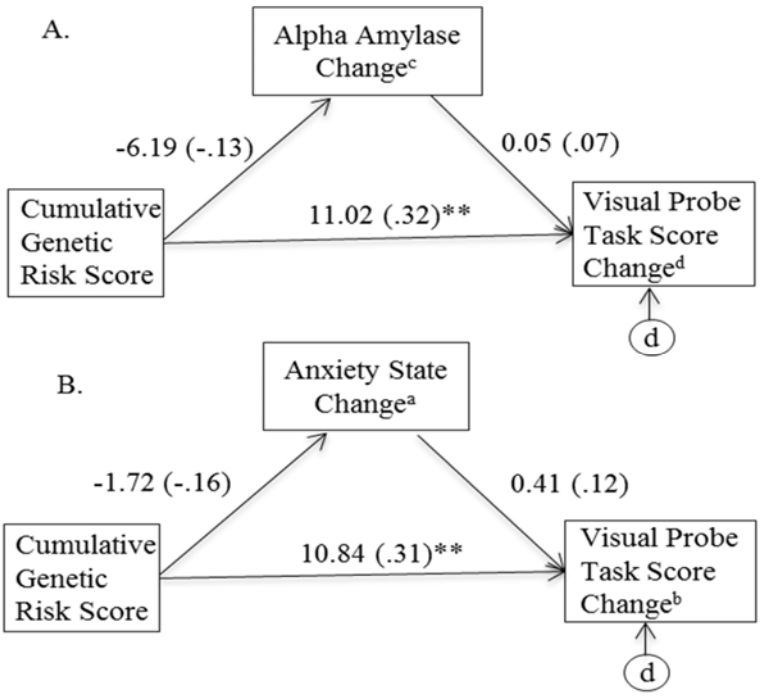

Figure 4. Regression analyses to test mediating roles of alpha amylase and anxiety state in the GCS x experimental condition on visual probe task score.

[a, b, c, d] Change between control and stress conditions, Unstandardized (standardized) coefficients are shown; sex was controlled for in all analyses (paths are not shown),

** $p < .01$.

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BOOK CHAPTER

Kim, J. (In Press). Substance addiction counseling, Handbook of substance and behavioral addiction counseling. Korean Addiction Counseling Association Publication.