A Variable-Number-of-Tandem-Repeats Polymorphism in the Dopamine D4 Receptor Gene Affects Social Adaptation of Alcohol Use: Investigation of a Gene-Environment Interaction

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Abstract

Research suggests that people adapt their own drinking behavior to that of other people. According to a genetic-differences approach, some individuals may be more inclined than others to adapt their alcohol consumption level to that of other people. Using a 3 (drinking condition) × 2 (genotype) experimental design (N = 113), we tested whether susceptibility to alcohol-related cues (i.e., seeing someone drink) was related to the variable number of tandem repeats in exon 3 of the D4 dopamine receptor gene. A strong gene-environment interaction showed that participants carrying at least one copy of the 7-repeat allele consumed substantially more alcohol in the presence of a heavy-drinking individual than did participants without this allele. This study highlights that individual variability in sensitivity to other people's drinking behavior may be attributable to genetic differences. Carrying the 7-repeat allele may increase the risk for heavy alcohol use or abuse in the company of heavy-drinking peers.

Alcohol consumption often takes place at bars, discos, night clubs, and parties—settings that are packed with alcohol-related cues, such as beverage marketing, advertisements, drinks placed on a bar, and other people drinking alcoholic beverages. Noticing the drinking patterns of other people sets norms that are used as guidelines for a person's own drinking pattern: the choice between drinking alcoholic or nonalcoholic beverages; the type of alcoholic beverage preferred; and the frequency, amount, and speed of drinking. Research demonstrates that people indeed show a remarkable level of adaptation to other people's drinking behavior (Bot, Engels, Knibbe, & Meeus, 2007; Larsen, Engels, Granic, & Overbeek, 2009; Quigley & Collins, 1999). Experimental and observational studies demonstrate that individuals who drink alcohol together often match one another in terms of what beverages they drink, how much they drink, and the pace at which they drink (Bot et al., 2007; Caudill & Kong, 2001; Caudill &

Marlatt, 1975; Collins, Parks, & Marlatt, 1985; Larsen et al., 2009; Quigley & Collins, 1999).

Nevertheless, there are individual differences in the extent to which people are susceptible to these social drinking cues. In heavy-drinking contexts, such as bars and fraternity parties, some individuals appear to base their alcohol consumption entirely on that of their company, whereas others follow their own pattern of drinking (Larsen et al., 2009). According to Shanahan and Hofer (2005), social contexts can trigger a genetic predisposition. Hence, individual differences in susceptibility to drinking cues might be related to genetic makeup.

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One of the most salient alcohol-related cues that can trigger the experience of craving alcohol is being in the company of individuals who are consuming alcohol (Franken, Rosso, & van Honk, 2003). The consumption of alcohol activates the mesolimbic dopamine system and increases dopamine levels in the brain, resulting in a pleasant, rewarding feeling (Berridge & Robinson, 1998). According to the incentive-sensitization model, with alcohol use becoming more regular, the brain learns that besides alcohol consumption, alcohol-related cues also are related to the rewarding effect of alcohol. Subsequently, the encounter of alcohol-related cues can induce incentive salience (i.e., wanting) for alcohol, by activating the mesolimbic dopamine system (Robinson & Berridge, 1993). The urge to drink thus results from a release of dopamine in the brain, which is generated in response to alcohol-related cues (Hutchison, McGeary, Smolen, Bryan, & Swift, 2002; Robinson & Berridge, 1993). The dopamine D4 receptor gene (*DRD4*) appears relevant to the expression of incentive salience (Berridge & Robinson, 1998; Hutchison et al., 2002). The 7-repeat allele of a 48-base-pair variable-number-of-tandem-repeats (VNTR) polymorphism in exon 3 of *DRD4* is associated with craving induced by alcohol cues, such as pictures or smell (Hutchison et al., 2002).

Hutchison et al. (2002) investigated whether the *DRD4* VNTR polymorphism moderated the effects of alcohol on craving. Their results suggested that participants carrying seven or more repeats of the *DRD4* VNTR (i.e., carriers of the 7-repeat allele) demonstrated higher craving after consumption of alcohol than participants without the *DRD4* 7-repeat allele. However, whether actual drinking behavior in social contexts also depends on whether individuals carry the *DRD4* VNTR 7-repeat allele remains to be examined. Therefore, in the current study, we investigated whether the *DRD4* VNTR polymorphism distinguishes individuals who are more versus less likely to adapt to another person's alcohol use, especially in a heavy-drinking context. A 3 (confederate's alcohol use: nondrinking, light drinking, or heavy drinking) × 2 (*DRD4* genotype: homozygous or heterozygous for the 7-repeat allele vs. no 7-repeat allele) between-participants design was used. We expected that carriers of the *DRD4* 7-repeat allele (*n* = 31) would drink more alcohol in the heavy-drinking condition than would noncarriers (*n* = 82).

Method

Participants and procedure

The participants were 113 Caucasian young adults (60 women and 53 men) who were invited to take part in a "study on an alcohol-prevention campaign" (this description was a cover for the real aim of the study). Participants were recruited at the Radboud University Nijmegen campus and were 21 years old on average (range: 18–28 years, *SD* = 2.39 years). Participants consumed an average of 14 alcoholic beverages per week (*SD* = 15.19). Abstainers were not included in the study.

All sessions were conducted between 4 p.m. and 9 p.m. and took place in a laboratory bar (a room furnished as an ordinary Dutch pub) at the Radboud University Nijmegen (Bot et al., 2007; Bot, Engels, Knibbe, 2005; Larsen et al., 2009). Ten undergraduate students were employed as confederates. Confederates and participants were always of the same sex, and confederates were instructed on their drinking behavior before the sessions began. Each participant-confederate pair was tested separately, and participants and confederates did not know each other. (For more detailed information about the procedure, see Larsen et al., 2009). Before the sessions started, participants completed an informed-consent statement and a medical checklist. Only participants who were healthy were included in the study, and pregnant women were excluded. Saliva samples were collected for DNA isolation using Oragene kits (Genotek, Ottawa, Ontario, Canada).

Participants met their coparticipants (i.e., confederates) and entered the laboratory bar. They evaluated five general commercial advertisements for 10 min. This was a neutral task (not part of the study) carried out as part of the cover story. Next, there was a 30-min break. During the break, participants and confederates were asked to sit at the bar, where peanuts and alcoholic and nonalcoholic drinks (i.e., beer, rosé, red or white wine, soda, and mineral water) were available. They were told they were allowed to drink whatever they wanted during the break. Confederates were preinstructed to drink two sodas (control condition), one alcoholic drink and then one soda (light-drinking condition), or three (women) or four (men) alcoholic drinks (heavy-drinking condition).

Confederates were trained to immediately place their order and to take the initiative in ordering subsequent drinks, so it was possible to observe whether participants would follow their lead by making the same choices. No bartender was present, so as to avoid interference in the interactions between participants and confederates. The experimenter did not indicate how long the break would last, unless the participant specifically asked about the length of the break. During each session, video and audio recordings were made with a flexible camera with zoom. A research assistant operated the camera in an observation room adjacent to the laboratory bar. After the break, participants evaluated a Dutch alcohol-abuse-prevention campaign. This evaluation was part of the cover story; the break during which drinking behavior was observed was the main focus of the study. Participants were debriefed after the data collection was completed. Participants received €12 for their participation, and those who had consumed alcohol were sent home by taxi. Protocols were approved by the Ethical Committee of the Faculty of Social Sciences, Radboud University Nijmegen.

Measures

DRD4 genotyping. The 48-base-pair direct repeat polymorphism in *DRD4* was genotyped by amplifying 10 ng of genomic DNA in a 10-μl volume with the following

components: 0.05 μM of fluorescently labeled forward primer VIC-5′-GCGACTACGTGGTCTACTCG-3′ (Applied Biosystems, Nieuwerkerk aan de IJssel, The Netherlands), reverse primer 5′-AGGACCCTCATGGCCTTG-3′, 0.4 mM of deoxynucleoside triphosphates (dNTPs), and 0.5 U of La Taq (Takara, Lonza Verviers S.p.r.l., Verviers, Belgium). These were in a GC I buffer (Takara, Lonza Verviers S.p.r.l.) with 1 M betaine. The cycling conditions for amplification involved 1 min at 94 °C, 35 cycles of 30 s at 94 °C, 30 s at 58 °C, and 1 min at 72 °C, with an additional 5 min at 72 °C. The length of the alleles was determined by direct analysis on an automated capillary sequencer (ABI3730, Applied Biosystems, Nieuwerkerk aan de IJssel, The Netherlands). Hardy-Weinberg equilibrium proportions were estimated, and no deviations from these proportions were found ($p = .76$). Participants' *DRD4* genotype was dummy-coded into two categories: 7-repeat allele carriers, with at least one long (7-repeat) allele, and noncarriers, who were homozygous for the short (fewer than 7 repeats) allele (Lichter et al., 1993).

Standardized alcohol consumption. All sessions were recorded and stored on DVDs. Three independent coders (undergraduate research assistants) monitored the sessions, and 15 of the 113 sessions were monitored by all three coders so that we could assess the reliability of their coding. The interrater correlations ranged from .90 to 1.00, indicating a high level of agreement among the three independent observers.

Total alcohol consumption was assessed by counting the number of alcoholic drinks consumed in the ad lib drinking session. Our dependent variable was the number of glasses of standardized alcohol consumption. One bottle of beer (5% alcohol) had a total volume of 170 ml and 8.5 ml of pure alcohol. One glass of wine (12.5% alcohol) had a total volume of 110 ml and 13.8 ml of pure alcohol. Because participants had to consume more beer than wine to imbibe the same amount of pure alcohol, we divided the total amount of beer consumed per participant by 1.62 in order to equalize the drinks in terms of pure alcohol content (Bot et al., 2005; Larsen et al., 2009).

Weekly alcohol consumption. Weekly alcohol consumption was measured with a self-report questionnaire that asked on which of the previous 7 days the respondent had consumed alcohol and how many drinks had been consumed on each of those days. The total number of drinks consumed over the 7 days was used in the analyses (Hajema & Knibbe, 1998).

Results

Means and standard deviations for observed and self-reported alcohol consumption are displayed in Table 1. Independent *t* tests showed that men consumed more alcohol per week than women. Men did not consume more alcohol in the observational sessions than women when the differences in pure alcohol content were taken into account (i.e., standardized drinks). There was a positive correlation between weekly drinking and observed drinking (standardized drinks: $r = .28$, $p < .01$; unstandardized drinks: $r = .43$, $p < .001$).

To determine whether participants' general drinking behavior (as a measure of weekly drinking) was randomly distributed across conditions, we conducted an analysis of variance. There was no difference in weekly drinking between the experimental conditions, $F(2, 112) = 0.38$, $p = .68$. Thus, participants' general drinking behavior was equally distributed across the experimental conditions.

Analysis of variance with factors of drinking condition, *DRD4* genotype, and participants' sex revealed a marginally significant effect of participants' sex on observed alcohol consumption, $F(1, 106) = 3.53$, $p = .06$, $\eta_p^2 = .03$, with men ($M = 0.76$, $SE = 0.10$) consuming more alcohol than women ($M = 0.50$, $SE = 0.10$). As predicted, the experimental drinking condition (i.e., the confederate's drinking level) and the *DRD4* VNTR polymorphism had a significant interactive effect on observed alcohol consumption, $F(2, 106) = 6.26$, $p = .003$, $\eta_p^2 = .11$ (Fig. 1). Simple-effects analysis demonstrated a difference in drinking in the heavy-drinking condition between carriers and noncarriers of the *DRD4* 7-repeat allele, $F(1, 34) = 7.12$, $p < .01$, $\eta_p^2 = .17$. In this condition, carriers consumed more than twice as many glasses of alcohol ($M = 1.79$, $SE = 0.23$) as noncarriers ($M = 0.82$, $SE = 0.14$).

To rule out the effect of participants' prior drinking history, we conducted an analysis controlling for the main effect of participants' amount of weekly drinking. Results of this

Table 1. Female and Male Participants' Self-Reported and Observed Drinking Behavior (Number of Drinks)

			Gender comparison				
	Total		Men		Women		
Measure	M	SD	M	SD	M	SD	t test
Self-reported weekly drink consumption	13.94	15.18	20.36	18.84	8.26	7.40	$t(113) = 4.63$**
Observed drink consumption in the lab (standardized)	0.56	0.85	0.71	0.84	0.44	0.85	$t(113) = 1.74$
Observed drink consumption in the lab (unstandardized)	0.95	1.48	1.52	1.81	0.48	0.89	$t(111) = 3.97$**

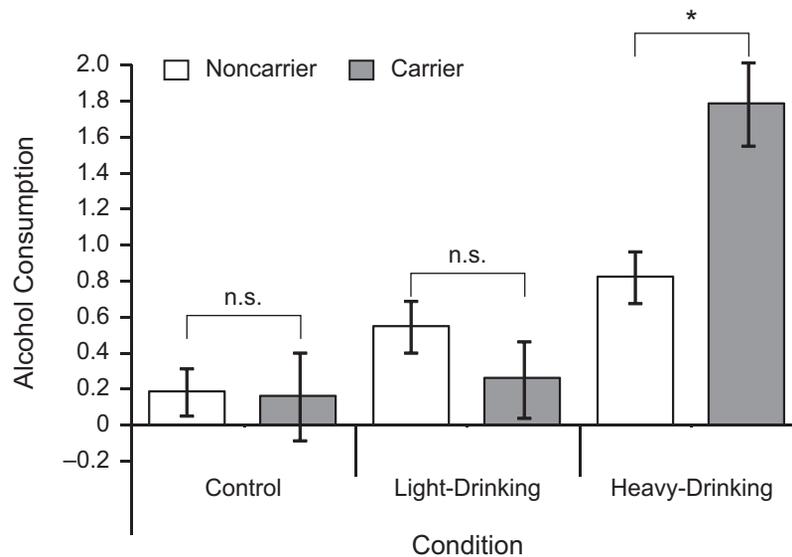Note: N = 113 (53 men and 60 women).
**$p < .001$.

Fig. 1. Mean alcohol consumption (standardized number of drinks) as a function of experimental condition and carrier status regarding the variable-number-of-tandem-repeats polymorphism of the dopamine D4 receptor gene (*DRD4*). Participants classified as carriers had one or more copies of the 7-repeat allele, and noncarriers had fewer than 7 repeats on both alleles. Error bars reflect standard errors of the mean. The control condition included 29 noncarriers and 9 carriers, the light-drinking condition included 26 noncarriers and 12 carriers, and the heavy-drinking condition included 27 noncarriers and 10 carriers. An asterisk indicates a significant difference between *DRD4* genotypes ($p < .01$).

analysis of covariance were similar to those of the original analyses: There was an interaction between drinking condition and the *DRD4* polymorphism, $F(2, 105) = 6.06$, $p = .003$, $\eta_p^2 = .10$.

Discussion

Our results showed that individual variability in sensitivity to other people's drinking behavior was strongly associated with the *DRD4* 7-repeat polymorphism. Although the precise neural and behavioral role of this genetic locus requires further exploration, this study demonstrates that *DRD4* 7-repeat carriers may be more attuned to, and influenced by, another person's heavy drinking behavior than noncarriers are. This effect can be explained by the blunted response of dopamine D4 receptors among *DRD4* 7-repeat carriers, which, because of elevated cyclic adenosine monophosphate (cAMP) levels, might augment dopamine signals after exposure to alcohol-related stimuli (Asghari et al., 1995; Robinson & Berridge, 1993; Stoof & Kebabian, 1981). Consequently, these individuals may experience a stronger urge to drink due to an enhanced dopamine response when in the company of heavy-drinking peers (Hutchison et al., 2002; Robinson & Berridge, 1993). It is important, though, to mention that because there was no difference in drinking in the light-drinking condition between individuals with and without the *DRD4* 7-repeat allele, this increased craving pertains only to the heavy-drinking condition.

The finding of this study extends previous research by suggesting that the role of the *DRD4* VNTR polymorphism not only concerns craving for alcohol, but also is related to social-influence processes on drinking. Hutchison et al. (2002) found that participants carrying the *DRD4* 7-repeat allele reported higher craving for alcohol after alcohol consumption than did participants who did not carry the *DRD4* 7-repeat allele. However, that study did not include the social aspects of alcohol consumption. The current study is the first to investigate whether people with the *DRD4* 7-repeat allele are more sensitive than those without the allele to social drinking cues (i.e., seeing someone drink) in an ecologically valid ad lib drinking context. One of the greatest strengths of this approach is its ecological validity. The experimental context closely simulated a real-life drinking situation; thus, our results are generalizable to the most typical social-drinking contexts (e.g., bars, restaurants, parties).

Despite the strengths and potential compelling implications associated with the current results, it is critical to emphasize that these results are preliminary and require replication before being implemented in clinical and public-health practices (Risch et al., 2009). Meta-analyses have demonstrated that studies examining gene-environment interactions associated with pathological outcomes do not always succeed in replicating previous findings (Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). Also, it has been suggested that some findings might be based on chance (Munafò et al., 2009) and that genetics often contribute only moderately to the explanation of human traits (Eaves, 2009). Therefore, we want to

underline the crucial importance of replicating the current findings, and the findings of gene-environment studies in general, to prevent drawing false-positive conclusions (see also van der Zwaluw & Engels, 2009).

Carrying the *DRD4* 7-repeat genotype may increase the risk for extensive alcohol use or abuse when spending time with heavy-drinking peers. If our experimental results are replicated, the implications are potentially far-reaching. Specifically, theories of alcohol use and abuse may be profoundly improved by combining genetic and social mechanisms into one overarching model. In turn, these improved, more complex theoretical models can lead to more targeted, effective, and cost-efficient prevention and treatment practices (Chakravarti & Little, 2003).

The current study corroborates the theoretical notion that social environments may trigger a genetic predisposition toward a certain behavior (Shanahan & Hofer, 2005) by demonstrating that individuals carrying the *DRD4* 7-repeat allele appear more sensitive than noncarriers to other people's drinking behavior. Whether or not people are wired to adapt their drinking to the choice and pace of others may partly depend on their genetic susceptibility to drinking cues. Future research should attempt to replicate this finding.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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