Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1 G-allele

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This study investigated whether automatic approach action tendencies for alcohol-related stimuli were associated with variation in the mu-opioid receptor gene (OPRM1), previously related to rewarding effects of alcohol and craving. An adapted approach avoidance task was used, in which participants pulled or pushed a joystick in reaction to the format of a picture shown on the computer screen (e.g. pull landscape pictures and push portrait pictures). Picture size on the screen changed upon joystick movement, so that upon a pull movement picture size increased (creating a sense of approach) and upon a push movement picture size decreased (avoidance). Participants reacted to four categories of pictures: alcohol-related, other appetitive, general positive and general negative. The sample consisted of 84 heavy drinking young men without a g-allele in the A118G (or A355G) single nucleotide polymorphism of the OPRM1 gene and 24 heavy drinking young men with at least one g-allele. Heavy drinking carriers of a g-allele showed relatively strong automatic approach tendencies for alcohol (approach bias). Unexpectedly, they also showed an approach bias for other appetitive stimuli. No approach bias was found for general positive or negative stimuli. These results suggest that automatic approach tendencies in response to appetitive stimuli could play a role in the etiology of addictive behaviors and related disorders. Further research is needed to investigate the specificity of this approach bias and possible gender differences.

Keywords: Alcohol, approach, avoidance, endophenotype, implicit cognition, OPRM1

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Introduction

Addictive behaviors are among the greatest causes of premature mortality worldwide (Goldman et al. 2005). A central paradox in the psychology of addiction is why self-destructive behaviors are continued despite knowledge of the harms (Wiers & Stacy 2006b). Research on implicit or automatic processes provides clues to understanding this paradox. This perspective has been accompanied by dual process models of addictive behaviors (Wiers & Stacy 2006a). In these models, addictive behaviors are influenced by two semi-independent systems: a fast associative ‘impulsive’ system, in which stimuli are automatically evaluated in terms of their motivational significance that automatically triggers a motivational orientation (approach or avoid), and a slower ‘reflective’ system, which includes controlled processes related to conscious deliberations and emotion regulation (Deutsch & Strack 2006; Stacy et al. 2004; Wiers et al. 2007). There is evidence that different neural structures underlie these processes (e.g. Bechara et al. 2006). There is also emerging evidence that the combination of strong appetitive processes and weak executive control predict alcohol misuse in youth (Grenard et al. 2008; Thush et al. 2008).

The associative process central in this study concerns the automatically triggered action tendency to approach or avoid a stimulus. Action tendencies are assessed with a new variety of a recently developed joystick task, the Approach–Avoidance Task (AAT; Rinck & Becker 2007). The rationale behind joystick-tasks is that arm flexion (pulling) is related to more positive evaluations than extension (pushing) (Cacioppo et al. 1993; see Palfai 2006 for an application to alcohol). In the AAT used here, pictures in one format were pulled and pictures in another format pushed, irrespective of picture contents. Reliable differences in pulling vs. pushing in relation to contents category (e.g. alcohol) can be interpreted as relatively automatic action tendencies (De Houwer 2003). With different (less implicit) tasks, it has already been shown that heavy but not light drinkers show automatic approach tendencies for alcohol (Field et al. 2005, 2008; Palfai & Ostatin 2003).

We investigated whether approach tendencies for alcoholic drinks were related to the A118G (or asn40asp) single nucleotide polymorphism (SNP) of the mu-opioid receptor gene (OPRM1). Note that the designation of this SNP has changed to A355G (Asn102Asp) because the OPRM1 protein may contain an additional 62 amino acids. For clarity we refer to this SNP as A118G. This polymorphism has an impact on β-endorphin receptor binding or expression (Bond et al. 1998; van der ZwaluW et al. 2007; Zhang et al. 2007). Carriers of a g-allele in this SNP reported stronger alcohol effects (Ray & Hutchison...
0.2 mM dNTPs, 0.1 NATOR v3.1 Ready Reaction Mix, 3 drinkers without a g-allele. automatic approach tendencies to alcohol pictures than heavy genes, Brain and Behavior (2009) 8: 101–106.

Materials and methods

Participants

Heavy drinking male participants were recruited from Maastricht University (all faculties except psychology) and from vocational colleges in the Maastricht neighborhood. Participants were recruited through publicity on college and university boards and with flyers. Interested students e-mailed and left their telephone number. In a brief telephone interview they were given more information about the study and screened for exclusion and inclusion criteria. Inclusion criteria were: male, age between 18 and 28 years (mean age 21) and Dutch origin, and drinking 20 or more standard alcoholic drinks per week, including at least one binge during the past 2 weeks. Exclusion criteria were dyslexia and colorblindness. A total of 109 participants were included, who took part in a larger study in which they were genotyped from buccal cells from the mouth, and exposed to alcohol cues (van den Wildenberg et al. 2007). The study was approved by the Medical Ethics Committee of the Academic Hospital Maastricht. Participants received €15 for participation. [We also attempted to include a group of light drinking males, who were drinking less than 11 drinks a week without binges during the past 2 weeks and were not complete abstainers. Unfortunately, this group proved extremely difficult to recruit from the college populations, especially because of the exclusion criterion of one or more binges during the past two weeks, which underscores the prevalence of binge drinking in this population (van de Luitgaarden et al. 2008; Wiers et al. 2006). In the same period in which over 100 heavy drinkers were included, we could include only 10 light drinkers. Therefore, this group is left out of the analyses here. Their AAT data showed no indication of an approach bias for any category of pictures.]

Genotyping

Genomic DNA was isolated from buccal cells (2 Omniswabs per sample; Den Bosch Whatman, The Netherlands) with the QIAamp DNA Mini Kit (Qiagen, Venlo, The Netherlands). For both procedures, the manufacturer protocols were followed. DNA concentration and purity were measured with a Nanodrop spectrophotometer. Determination of the OPRM1 A118G SNP of the OPRM1 gene would show stronger automatic approach tendencies to alcohol pictures than heavy drinkers without a g-allele.

a total volume of 20 μl in a Biometra T1 thermocycler. Cycling conditions are according to the manufacturer’s protocol. Extension products were purified by ethanol precipitation following the manufacturer’s procedure and size resolved on an ABI3100 Genetic Analyzer, using 36-cm capillaries filled with POP6 polymer. The sequence traces were analyzed using SEQUENCING ANALYSIS software version 3.7 (Applied Biosystems). Two researchers independently scored genotypes, and a third expert judged discordant results before entering them into the database. This procedure led to an agreement of 100%. The allele frequencies observed in this study were in conformity with Hardy–Weinberg equilibrium expectations, χ(2) = 0.18, P > 0.50.

Instruments

Alcohol use and problems

Alcohol use was measured with a self-report questionnaire (Wiers et al. 1997) based on the timeline follow-back method (Sobell & Sobell 1990). For every day of the past week, participants indicated whether they consumed an alcoholic drink, in which circumstances, which drinks and how many standard consumptions of each drink. In addition, they indicated the number of occasions on which they had drunk five or more standard glasses of alcohol during the past 2 weeks (binge). Alcohol-related problems were assessed with the Rutger Alcohol Problem Index (RAPI) and the Alcohol Use Disorders Identification Test (AUDIT). The RAPI is a self-report questionnaire to measure problems and problematic situations adolescents and young adults have experienced with alcohol (White & Labouvie 1989). The AUDIT is also a self-report instrument that provides information about heavy alcohol use, symptoms of alcohol dependence and alcohol-related problems. The questionnaire consisted of 10 items and is used to identify persons whose alcohol consumption patterns may put them at risk for alcohol-related harm (Saunders et al. 1993). A cut-off score of 8 is used to identify hazardous drinking, and in students a cut-off of 11 has been proposed to identify likely alcohol use disorders in students (Fleming et al. 1991). Here, 85% of participants scored 8 or higher and 70% 11 or higher (median was 13).

Approach–avoidance task

Participants performed our new alcohol variety of the Approach Avoidance Task (Rinck & Becker 2007). Four categories of stimuli were used: alcohol and shape- and color-matched other appetitive pictures (primarily soft drinks but also a ketchup bottle as a match for a red bottle of a popular premix drink; see Appendix S1), and general negative pictures containing animals and humans, from the International Affective Picture System (IAPS; Lang et al. 2005, see Appendix S1 for exact picture numbers). Each category consisted of 10 pictures, with both a variety in portrait and one in landscape format. When the joystick was pulled, the picture grew bigger and when it was pushed it grew smaller (Fig. 1; for technical details see Rinck & Becker 2007). This ‘zooming-feature’ in itself already generates a sensation of approach or avoidance, respectively (Neumann & Strack 2000). Hence, the AAT combines the proprioceptive (arm movement) and exteroceptive (zooming feature) cues of approach and avoidance. Combining these features also serves to disambiguate the joystick task: without the zooming feature, some participants interpret movements in the opposite way as intended, taking the object instead of their own body as reference point. For example, an arm extension in response to a picture of a beer can be interpreted as a movement away from the body (avoidance) or as an approach of the beer and with the zooming feature this is no longer the case (Rinck & Becker 2007).

First, 10 practice trials were presented: neutral gray rectangles in landscape or portrait format. Format movement assignments were counterbalanced (half of the participants pulled pictures that came in landscape format and pushed portrait pictures and half of the participants received the opposite instruction). The 80 test pictures were presented in quasi-random order (maximally three pictures of one category in a row and three pictures of the same format). Error percentages above 25% and mean reaction times (RT) longer than 3 SD (120.94 ms) were discarded as outliers (6 AA participants). The AAT difference scores were calculated as the median RT for pushing
AAT index denotes a positive value, hence an approach bias. As compared to results from previous studies using different tests of approach vs. avoidance tendencies (approach tendencies had already shown that approach tendencies were stronger and homogenous in male heavy drinkers with or without a g-allele in the A118G SNP of the \textit{OPRM1} gene), the study was that carriers of the g-allele showed an automatic approach bias (positive AAT score) both in response to alcohol pictures and in response to other appetitive pictures (both biases were significantly different from zero, \(P < 0.05\)). Carriers of the g-allele did not show this approach bias for general positive pictures, or an avoidance bias for general negative pictures (\(P > 0.05\)). Heavy drinkers without a g-allele did not show an approach bias for any category of stimuli (\(P > 0.10\)).

We performed a number of control analyses. First, it was investigated whether the genotype-related difference in automatic approach tendencies had already shown that approach tendencies were stronger and homogenous in male heavy drinkers with or without a g-allele in the A118G SNP of the \textit{OPRM1} gene, the study was that carriers of the g-allele showed an automatic approach bias (positive AAT score) both in response to alcohol pictures and in response to other appetitive pictures (both biases were significantly different from zero, \(P < 0.05\)). Carriers of the g-allele did not show this approach bias for general positive pictures, or an avoidance bias for general negative pictures (\(P > 0.05\)). Heavy drinkers without a g-allele did not show an approach bias for any category of stimuli (\(P > 0.10\)). We performed a number of control analyses. First, it was investigated whether the genotype-related difference in automatic approach tendencies had already shown that approach tendencies were stronger and homogenous in male heavy drinkers with or without a g-allele in the A118G SNP of the \textit{OPRM1} gene, the study was that carriers of the g-allele showed an automatic approach bias (positive AAT score) both in response to alcohol pictures and in response to other appetitive pictures (both biases were significantly different from zero, \(P < 0.05\)). Carriers of the g-allele did not show this approach bias for general positive pictures, or an avoidance bias for general negative pictures (\(P > 0.05\)). Heavy drinkers without a g-allele did not show an approach bias for any category of stimuli (\(P > 0.10\)). We performed a number of control analyses. First, it was investigated whether the genotype-related difference in automatic approach tendencies had already shown that approach tendencies were stronger and homogenous in male heavy drinkers with or without a g-allele in the A118G SNP of the \textit{OPRM1} gene, the study was that carriers of the g-allele showed an automatic approach bias (positive AAT score) both in response to alcohol pictures and in response to other appetitive pictures (both biases were significantly different from zero, \(P < 0.05\)). Carriers of the g-allele did not show this approach bias for general positive pictures, or an avoidance bias for general negative pictures (\(P > 0.05\)). Heavy drinkers without a g-allele did not show an approach bias for any category of stimuli (\(P > 0.10\)). We performed a number of control analyses. First, it was investigated whether the genotype-related difference in automatic approach tendencies had already shown that approach tendencies were stronger and homogenous in male heavy drinkers with or without a g-allele in the A118G SNP of the \textit{OPRM1} gene, the study was that carriers of the g-allele showed an automatic approach bias (positive AAT score) both in response to alcohol pictures and in response to other appetitive pictures (both biases were significantly different from zero, \(P < 0.05\)). Carriers of the g-allele did not show this approach bias for general positive pictures, or an avoidance bias for general negative pictures (\(P > 0.05\)). Heavy drinkers without a g-allele did not show an approach bias for any category of stimuli (\(P > 0.10\)).

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**Results**

**Genotyping**

Genotyping resulted in 84 participants homozygous for the major A allele, 23 participants with the AG combination and 1 participant homozygous for the G allele. One participant was genotyped as AAG. Because the presence of three alleles indicates a possible duplication of part of chromosome 6 or sample contamination, this subject was excluded from the analyses. So, allele frequency was 0.88 for the A allele and 0.12 for the G allele. In the analyses, the data of the AG and GG participants were combined.

**Automatic action tendencies**

Differences between pushing and pulling median RTs (AAT scores or approach biases) were examined with a mixed \textit{ANOVA} with OPRM1 genotype (AA vs. AG/GG in the A118G SNP of the \textit{OPRM1} gene) as between-subjects factor, and picture type as a within-subjects factor with four levels (alcohol, control appetitive (primarily soft drinks), general appetitive and general negative pictures). The two separate lines represent heavy drinkers subdivided by OPRM1 genotype (the A118G SNP of the \textit{OPRM1} gene). Heavy drinkers carrying a g-allele show an automatic approach bias (positive value) for alcohol and other appetitive pictures, not for general positive or negative pictures.

![Approach bias](image)

Figure 1: Difference in reaction times between pushing (avoid) and pulling (approach) for the four categories of pictures: alcohol, control (color- and form-matched pictures, mostly soft drinks), general positive and general negative pictures. The two separate lines represent heavy drinkers subdivided by OPRM1 genotype (the A118G SNP of the \textit{OPRM1} gene). Heavy drinkers carrying a g-allele show an automatic approach bias (positive value) for alcohol and other appetitive pictures, not for general positive or negative pictures.

minus the median RT for pulling (in keeping with the original publication on this measure and related RT tests (MacLeod et al. 2002), we analyzed the median RTs, which are less sensitive to outliers than means (Rinck & Becker 2007)). A positive value on the AAT index denotes a positive value, hence an approach bias.

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We performed a number of control analyses. First, it was investigated whether the genotype-related difference in automatic approach tendencies had already shown that approach tendencies were stronger and homogenous in male heavy drinkers with or without a g-allele in the A118G SNP of the \textit{OPRM1} gene. Main outcome of the study was that carriers of the g-allele showed an automatic approach bias for alcohol and for other appetitive stimuli, not found in heavy drinkers without a g-allele. There was some specificity to this finding: no significant approach bias was found for general positive or negative stimuli. Previous studies using different tests of approach vs. avoidance tendencies had already shown that approach tendencies for alcohol were found in heavy but not in light drinkers (Field \(et al.\) 2005, 2008; Palfai & Ostafin 2003), which was also not the case in our small sample of light drinkers (see methods).
In line with our previous findings regarding subjective craving (van den Wildenberg et al. 2007) and findings on subjective alcohol effects (Ray & Hutchison 2004), we hypothesized that g-allele carriers would show an approach bias specifically to alcohol cues, but we found an equally large bias for other appetitive stimuli (primarily soft drinks). This finding could indicate that carriers of a g-allele have stronger appetitive reactions in general, not only to alcohol. In line with this interpretation, strong appetitive reactions have been reported in g-allele carriers in response to other drugs, like heroin (Zhang et al. 2007) and suggestions for a more general role of opioids in relation to obesity have been made (Volkow & Wise 2005). Perhaps, carriers of a g-allele would also show stronger automatic appetitive reactions to other appetitive stimuli such as food or sex-related stimuli, but as far as we are aware, this possibility has not been evaluated yet. In line with this suggestion, recent neurobiological studies have pointed to the importance of mu-opioid neurotransmission in appetitive behavior: temporal increases in mu-opioid neurotransmission in 'hedonic hot spots' in the brain increase food consumption (Pecina et al. 2006). Furthermore, there is some evidence that carriers of a g-allele respond better to the opioid receptor antagonist naltrexone than alcohol-dependent patients without a g-allele (Anton et al. 2008; Oslin et al. 2003; Ray & Hutchison 2007), but findings have not been consistent (Gelernter et al. 2007). There are also some indications in the literature that naltrexone could be helpful in the treatment of obesity (Yeomans & Gray 2002), perhaps in that patient-group carriers of a g-allele would also profit more from naltrexone. In line with the present findings, the latter review concluded that opioid-mediated reward mechanisms are likely to play an important control in hedonic aspects of ingestion in general. However, a recent innovative study that combined genotyping with functional Magnetic Resonance Imaging (fMRI) found stronger hemodynamic responses in mesocorticolimbic areas after a prime dose of alcohol vs. juice in g-allele carriers, suggesting particularly strong appetitive reactions to alcohol (Filbey et al. 2008). Clearly further research into automatic responses to different categories of appetitive stimuli in relation to the OPRM1 gene is needed.

The measure of approach tendencies used here is new and an interesting feature is that it is more likely to tap automatic approach tendencies than the tasks previously used. The reason is that the version of the AAT used here can be categorized as an 'irrelevant feature' task (De Houwer 2003): participants are instructed to react to the format of the picture (landscape or portrait, cf. Huijding & De Jong 2005) with a push or pull movement, irrespective of the contents. In the other tasks used to assess approach bias, stimuli had to be explicitly categorized (e.g. alcohol or not alcohol). In the Implicit Association Test, this categorization is combined with either approach or avoid words (Ostafin & Palfai 2006; Palfai & Ostafin 2003), and in the Stimulus Response Compatibility test with a symbolic approach or avoidance movement (Field et al. 2005, 2008). When a reliable difference in approach vs. avoidance movements is found in response to a picture category in an irrelevant feature task, this is a strong indication that the responses are relatively automatic (De Houwer 2003). The difference in automatically triggered approach vs. avoidance tendencies found here for alcohol and other appetitive stimuli in carriers of a g-allele is noteworthy given the absence of such an effect for normatively positive and negative IAPS pictures. The latter finding is in line with other recent findings (Lavender & Hommel 2007; Rotteveel & Phaf 2004) who only found faster approach for positive stimuli and faster avoidance for negative stimuli when the task of the participant was to rate the valence of the stimuli, not when they reacted to an irrelevant feature of the stimuli, as in the present study. A possible explanation for the difference in effect on the appetitive stimuli and the general positive and negative stimuli (pictures of animals and humans) is that a push or pull movement with the arm may be more automatic for appetitive stimuli (which we typically bring to our mouth with an arm movement) than for human faces and animals. The lack of correlation between approach bias and subjective craving also indicates that these two are not identical: one may or may not become aware of a relatively automatic action tendency. One possibility is that subjective craving is more related to the control of an approach bias, which can be activated when the approach tendency is undesirable given the circumstances or other goals.

The present study is one of the first to associate relatively automatic processing biases that are thought to play a role in psychopathology to genetic variation. Two other studies found an association between another gene (serotonin transporter gene) and attentional bias: one study found an association between the 5HTT gene and attentional bias for smoking-related stimuli in smokers (Munafo et al. 2006), another between the same gene and an attentional bias for threat stimuli in psychiatric patients (Beever et al. 2007). In addition, several studies have found genetic associations with executive functions (review: Goldberg & Weinberger 2004). In view of recent dual process models of addiction (Deutsch & Strack, 2006; Wiers & Stacy 2006a,b), these findings suggest that genetic variability is likely to be related both to individual differences in relatively automatic appetitive responses and to individual differences in executive functions. In several recent behavioral studies, we found that individual differences in executive functions moderate the impact of automatic appetitive associations on alcohol use and misuse (Grenard et al. 2008; Thush et al. 2008). Therefore, it could be particularly interesting for future studies to include indices of both appetitive and executive control processes and candidate genes related to these different cognitive processes.

Although the study yielded interesting results, some limitations should be acknowledged. We included only heavy drinking males. We tried to include also a sufficient number of light drinking males, but this proved very difficult in our college population (see under methods). Given the fact that we only included males, it is unclear whether results would generalize to heavy drinking females. There are some indications that genetic variation related to endogeneous opioids (including beta-endorphine) may be particularly relevant for the development of addiction in men: sons but not daughters of multigenerational male alcoholics show a sharp rise in beta-endorphin after drinking alcohol, which was associated with experiencing a strong subjective "kick" directly after drinking alcohol (Gianoulakis et al. 1996). Furthermore, a study in nonhuman primates indicated that male but not female carriers of a g-allele in the OPRM1C77G allele showed greater...
alcohol preference related to individuals without a g-allele in this polymorphism related to the one studied here. However, human studies including both male and female heavy drinkers did not report sex differences, but statistical power may have played a role (Filbey et al. 2008; Ray & Hutchison 2004). Clearly, including females in a future study on automatic appetitive responses to different categories of appetitive stimuli would be particularly interesting. Finally, it should be noted that the \textit{OPRM1} gene has not been found to be associated with alcohol use disorders at the phenotypic level (Arias et al. 2006; van der Zwaluw et al. 2007). This may raise the question why this gene is still investigated in relation to addictive behaviors. The answer is that it is widely acknowledged that addictive behaviors are heterogeneous and consist of different subtypes that appear to have different developmental trajectories (Sher et al. 2005). Hence, it is perfectly possible that a gene is related to a neurocognitive process (e.g. enhanced appetitive reactions for drug-related stimuli), which plays a role in the development of addictive behaviors in a particular pathway, without being related to the overall phenotype. Perhaps relatively automatic appetitive responses, assessed with a reaction time test as used here or with fMRI responses to alcohol (Filbey et al. 2008) will constitute an intermediate phenotype or endophenotype (Gottesman & Gould 2003) related to a specific pathway to addictive behaviors.

In conclusion, the present study found that heavy drinkers with a g-allele in the A118G SNP of the \textit{OPRM1} showed relatively strong automatic approach reactions to alcohol as well as to other appetitive stimuli, not found in heavy drinkers without a g-allele. Further research is needed to determine whether this genetic difference is related to relatively strong appetitive responses in general or specifically for addiction-related stimuli, whether there is a sex difference in these responses and how they are related to the etiology of addictive behaviors.

References


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Acknowledgement

R.W.W. now holds a chair of developmental psychopathology at the department of psychology, University of Amsterdam. This study was carried out while the first author was still at the Department of Clinical Psychological Science, Maastricht University, Maastricht, The Netherlands, where M.D. and E.v.d.W. were also located at the time of the study. M.R. is at the Department of Clinical Psychology, Behavioural Science Institute, Radboud University, Nijmegen, The Netherlands. This research was supported by supported by Vidi grant 452.02.005 from the Dutch Organization for Scientific Research (NWO), awarded to the first author. We thank Gerard van Breukelen for statistical advise, Rob Janssen, Ellen Lambrixs and Hubert Smeets for genetic analyses and Susan Ames, Kenneth Sher, Alan Stacy, Frank Baas and two anonymous reviewers for helpful comments on the manuscript.

Supporting Information

Additional supporting information may be found in the online version of this article.

Appendix S1.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author.