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Depressive rumination and the C957T polymorphism of the *DRD2* gene

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Abstract Depressed individuals who ruminate have difficulties learning from punishment and suppressing task-irrelevant information. The C957T polymorphism of the *DRD2* gene, which affects functioning of D2 dopamine receptors (DRD2) that are expressed predominantly in the indirect pathway of the basal ganglia, has been found to influence suppression and punishment learning. Given these associations, we examined in the present study whether depressive rumination is related to the C957T polymorphism in 317 clinically depressed individuals and 317 never-depressed control individuals. A 2 × 2 (diagnostic group ×C957T polymorphism) analysis of variance conducted on depressive rumination scores yielded a significant interaction of group and C957T: Individuals with two 957C alleles reported higher levels of depressive rumination than did individuals with one or two 957T alleles if they were depressed, but not if they were healthy. The present findings suggest that the dopaminergic system and DRD2 are related to the frequency of maladaptive rumination in depressed individuals. Thus, DRD2 may be an important target for the pharmacological treatment of depressive rumination.

Keywords Rumination · Depression · *DRD2* · Genes · Dopamine · Basal ganglia

Introduction

Depressive rumination is defined as repetitive negative thinking focused on the causes, meanings, and implications of one's depressed mood (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Investigators using the Ruminative Response Styles (RRS) scale (Nolen-Hoeksema & Morrow, 1991) to measure depressive rumination have found that individuals differ in their tendency to respond to a depressed mood with rumination and, further, that these individual differences are stable over time (see Nolen-Hoeksema et al., 2008). Researchers have also demonstrated that rumination in depressed individuals typically leads to serious negative consequences, often worsening mood and impairing insight into problems (Nolen-Hoeksema et al., 2008). Moreover, depressed individuals who report a higher tendency to ruminate experience longer and more severe episodes of major depressive disorder (MDD) than do depressed individuals who report lower levels of rumination (Nolen-Hoeksema et al., 2008).

Investigators have established that depressive rumination is also related to a number of cognitive deficits. For example, researchers have found that a tendency to ruminate is related to difficulties suppressing task-irrelevant information in depressed individuals, but not in never-depressed controls (e.g., Joormann & Gotlib, 2008). Difficulties with suppression may allow negative maladaptive thoughts to be updated into working memory (WM) even when they are not relevant or wanted, explaining why depressed individuals with a high tendency to ruminate report that they often cannot control their rumination (Papageorgiou & Wells, 2001). Some evidence also suggests that depressed ruminators have difficulties learning from punishment. For example, Whitmer, Frank, and Gotlib (in press) recently reported that rumination in depressed individuals, but not in never-depressed controls, is related to difficulties avoiding stimuli that had been frequently punished in a training phase, but not to difficulties approaching stimuli that had been frequently rewarded. Difficulties learning from and avoiding punishment could lead individuals to engage in behavior that leads to more punishment, which, in turn, would increase both distress and rumination. Impaired

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punishment learning may also make it difficult for depressed individuals to realize that their ruminative thoughts are leading to punishing consequences, such as more negative mood, impaired problem solving, and decreased insight, which would also lead to more frequent rumination. Indeed, depressed individuals who report a high tendency to ruminate report that they engage in rumination because they believe that it is a positive way to cope with distress; in other words, despite evidence to the contrary, they continue to believe that their rumination improves insight into their problems, enhances their problem-solving ability, and eventually leads to more positive affect (e.g., Papageorgiou & Wells, 2001, 2003).

Although researchers examining cognitive aspects of rumination have made substantial progress over the past decade, investigators have only recently begun to identify the neural and genetic correlates of depressive rumination (e.g., Beevers, Wells, & McGeary, 2010; Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Hilt, Sander, Nolen-Hoeksema, & Simen, 2007; Vanderhasselt, Kuhn, & De Raedt, 2011). In the present study, we examined the hypothesis that the frequency of maladaptive rumination in depressed individuals is related to the C957T polymorphism of the DRD2 gene (*DRD2*). This polymorphism alters the translation and stability of D2 dopamine receptors (DRD2) that are expressed predominantly in the indirect pathway of the basal ganglia (BG; Duan et al., 2003), leading to decreased DRD2 availability in individuals with an increased number of 957C alleles, as compared with 957T alleles (Hirvonen et al., 2005, 2009). Importantly, a number of researchers have demonstrated that this polymorphism also affects cognitive processes that may exacerbate the frequency of rumination in depression. For example, investigators have found that individuals with an increased number of 957C alleles have greater difficulty learning from punishment, but not from reward, in a probabilistic selection task (Frank, Doll, Oas-Terpstra, & Moreno, 2009; Frank & Hutchison, 2009; Frank, Moustafa, Haughey, Curran & Hutchison, 2007), the same task used to identify deficits in punishment learning in depressed ruminators (Whitmer et al., in press). Other investigators have found that having an increased number of 957C alleles is associated with decreased suppression in an attentional blink task and that 957C homozygotes have greater difficulty controlling the contents of WM than do carriers of the 957T allele (Colzato, Slagter, Rover, & Hommel, 2011; Jacobsen, Pugh, Menci, & Gelernter, 2006). Although we did not examine suppression or punishment learning in the present study, we reasoned that if deficits in suppression and punishment learning contribute to rumination in depressed individuals, and if 957C-allele homozygotes have difficulties exerting suppression and learning from punishment, depressed individuals who are 957C-allele homozygotes are likely to exhibit higher levels of rumination than are depressed individuals with one or two 957T alleles.

We also examined the relation between the C957T polymorphism and frequency of rumination in a matched control group of never-depressed individuals. If our assumption that suppression and/or punishment learning mediate the relation between rumination and the C957T polymorphism is correct, it is likely that this relation is moderated by depression status. A number of investigators have found that rumination has fewer punishing consequences in nondepressed than in depressed individuals. For example, researchers have found that as compared with distraction inductions, rumination inductions lead to impaired problem solving, more negative mood, and more negative thinking in depressed, but not in nondepressed, individuals (see Nolen-Hoeksema et al., 2008, for a review). If rumination leads to lower levels of punishment in never-depressed individuals than in depressed individuals, the ability to learn from punishment or to suppress punishing thoughts should have less effect on the frequency of rumination in never-depressed than in depressed individuals. Therefore, if suppression and punishment learning do mediate the relation between the C957T polymorphism and rumination, the relation between the C957T polymorphism and rumination should be weaker in never-depressed than in depressed individuals. Again, it is important to emphasize that we are examining not suppression or punishment learning in the present study but, rather, the predictions of a formulation that suppression and punishment learning mediate the association between the C957T polymorphism and rumination.

Method

Participants

Six hundred eighty-one individuals (322 with MDD and 359 healthy controls) were recruited from the communities of Oakland, San Francisco, and San Jose. Participants were solicited through advertisements posted in numerous locations (e.g., Internet bulletin boards, university kiosks, supermarkets, etc.). Because allele frequency in the C957T polymorphism of the *DRD2* gene has been found to vary across race/ethnicity groups (National Center for Biotechnology Information, www.ncbi.nlm.nih.gov; identification number rs6277), we matched the race/ethnicity distribution of the MDD and control groups (Lee, 2004). To do so, before conducting the rumination analyses, we reduced the size of any ethnic group that was larger in the depressed or the never-depressed group by randomly excluding the appropriate number of participants from each ethnic group. This matching process left a final sample of 317 participants in both the MDD and control groups. The Structured

Clinical Interview for DSM (SCID; First, Spitzer, Gibbon, & Williams, 2001) was administered to all participants to assess current and lifetime diagnoses for axis-I disorders. The SCID has good reliability (e.g., Skre, Onstad, Torgersen, & Kringlen, 1991), and our team of trained interviewers has established excellent interrater reliability with the SCID (κ = .92; e.g., Gotlib et al., 2004; Levens & Gotlib, 2010). Individuals were excluded from participating in this study for alcohol/substance abuse or dependence in the past 6 months, social phobia, posttraumatic stress disorder, bipolar I or bipolar II, obsessive–compulsive disorder, a history of psychosis, and any learning disabilities that could interfere with their ability to perform a cognitive task. Participants who met DSM–IV criteria for current MDD were included in the depressed group, and participants with no current or past axis I disorder were included in the never-depressed control (CTL) group.

Measures

Depressive symptomatology

We administered the Beck Depression Inventory–II (BDI; Beck, Steer, & Brown, 1996) to all participants. The BDI is a 21-item self-report questionnaire that assesses the severity of depressive symptoms. This measure has high reliability and validity (e.g., Beck et al., 1996).

Depressive rumination

We measured depressive rumination with the five-item Brooding subscale of the RRS scale (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). The items are as follows: (1) Think "what am I doing to deserve this?"; (2) think "why do I always react this way?"; (3) think about a recent situation, wishing it had gone better; (4) think "why do I have problems other people don't have?"; (5) think "why can't I handle things better?" Participants rate how much they agree with each item, using a 4-point Likert scale: 1 = *almost never*; 2 = *sometimes*, 3 = *often*, 4 = *almost always*. The Brooding subscale has been consistently associated with maladaptive consequences of rumination, such as more negative mood (Nolen-Hoeksema et al., 2008). We did not examine the full RRS scale because most of the items on this scale are confounded with items from the BDI scale (Treynor et al., 2003). Treynor et al. also reported evidence, in a sample of unselected participants, of a second five-item Reflection subscale of the RRS scale that was not confounded with BDI items. However, Whitmer and Gotlib (2011) recently presented data that raised questions concerning the validity and reliability of this subscale in clinically depressed individuals and suggested that it is not appropriate to compare scores on the Reflection subscale of currently depressed and of never-depressed individuals. Moreover, it is not clear whether reflection is a subtype of rumination (Treynor et al., 2003) or whether rumination and reflection are two subtypes of the more general construct of repetitive self-focus (e.g., Nolen-Hoeksema et al., 2008; Trapnell & Campbell, 1999). In a recent review of the rumination literature, Nolen-Hoeksema et al. (2008) posited that rumination and brooding are synonymous terms. Thus, in this study, we operationalized depressive rumination as scores on the Brooding subscale of the RRS scale. The alpha coefficients for this subscale were .77 in the MDD group and .75 in the CTL group.

DNA extraction and genotyping

An Oragene DNA self-collection kit (DNA Genotek, Inc.) was used to obtain saliva samples for DNA extraction after participants completed the SCID. Applied Biosystems' TaqMan SNP Genotyping Assay (Assay ID# C_11229240_10) was used to genotype the C957T polymorphism of the *DRD2* gene (rs6277). Three genotype groups were formed for the C957T polymorphism: T-allele homozygotes, C/T-allele heterozygotes, and C-allele homozygotes. For the C and T alleles, sequence-specific primers for the Taqman assays were used (50-CTGTCGGGAGTGCTG-30 and 50-CTGTCAGGAGTGCTG-30) along with the reverse primer 50-GCCCATT-CTTCTCTGGTTTGG-30. The PCR reaction was carried out in a final volume of 15 μl consisting of 50 ng of genomic DNA, 50 ng each of sense and antisense primers, 7.5 ul of Taq PCR Master mix (Qiagen, Cat. #201445), and 10 % DMSO. The PCR conditions included an initial denaturation step at 95 C for 3 min, followed by 35 cycles of denaturation at 95 C for 30 s, annealing at 54 C for 45 s, and extension at 72 C for 1 min, with a final extension of 10 min at 72 C. The PCR products were digested at 37 C for 3 h with 5 U of the restriction enzyme MseI (New England Biolabs, Cat. #R0525L). The products were electrophoresed through 7 % Polyacrylamide gel (Acrylamide/bis-Acrylamide ratio 19:1) at 180 V for 40 min. A 50-bp marker was used to measure the fragments' size.

Results

Participant characteristics

Demographic and clinical characteristics of the depressed and never-depressed participants are presented in Table 1. Both the MDD and CTL groups consisted of 220 Caucasians, 26 Asian-Americans, 26 mixed-race (7 reporting partial Hispanic ethnicity), 20 African-Americans, 19 Hispanics, 4 Pacific Islanders, and 2 Native Americans. As was expected, as compared with the CTL group, the MDD group obtained significantly higher scores on the BDI, $t(632) = 34.9$, $p < .0001$. The breakdown of the C957T genotype (C/C:C/T:T/T) was 100:146:71 in the

Table 1 Demographic and clinical characteristics of the participants

	Depressed M (SD)	Never-depressed M (SD)
N (males)	317 (90)	317 (107)
Age	39.9 (11.8)	36.6 (12.1)
BDI	27.9 (11.8)	2.59 (5.3)
Depressive rumination	2.73 (.73)	1.43 (.47)
Number taking antidepressants	148	0

BDI, Beck Depression Inventory–II; Depressive rumination, scores on the brooding subscale of the Ruminative Response Styles scale

MDD group and 115:140:62 in the CTL group; the genotypes were in Hardy–Weinberg equilibrium (*p*s > .5).

DRD2 and rumination

A 2 (group: MDD vs. CTL) × 3 (C957T: CC vs. CT vs. TT) analysis of variance (ANOVA) conducted on depressive rumination scores yielded a significant main effect of group, $F(1, 628) = 645.38$, $p < .0001$, $\eta^2 = .507$: Depressed individuals reported higher tendencies to brood than did never-depressed controls (see Table 1). As was predicted, the ANOVA also yielded a significant main effect of C957T, $F(2, 628) = 5.084$, $p = .006$, $\eta^2 = .016$. Post hoc contrasts revealed that, as was expected, individuals with two C alleles reported significantly higher tendencies to ruminate ($M = 2.14$, $SE = .04$) than did individuals with only 1 957C allele ($M = 2.05$, $SE = .04$), $p < .001$, or with 2 957T alleles ($M = 2.07$, $SE = .05$), $p = .005$, who did not differ significantly from each other, $p = .852$. These main effects were qualified, however, by a significant interaction of group and C957T, $F(2, 628) = 6.648$, $p < .001$, $\eta^2 = .021$ (see Fig. 1).

To examine this interaction, we conducted separate one-way ANOVAs (by C957T) on the depressive rumination scores of the MDD and CTL participants. As can be seen in Fig. 1, there is little overlap of brooding scores between the depressed and control groups. The ANOVA conducted on the CTL group did not yield a significant effect of C957T, $F(2, 314) = 0.833$, $p = .436$, $\eta^2 = .005$. In contrast, the ANOVA conducted on the MDD group did yield a significant effect of C957T, $F(2, 314) = 7.74$, $p < .001$, $\eta^2 = .047$. Post hoc contrasts revealed that, as was expected, depressed individuals with two 957C alleles reported significantly higher tendencies to ruminate (2.96, $SE = .07$) than did depressed individuals with only 1 957C allele (2.66, $SE = .06$), $p < .001$, or with 2 957T alleles (2.56, $SE = .08$), $p < .0001$, who did not differ from each other, $p = .37$. A follow-up one-way (by C957T) analysis of covariance (ANCOVA) within the MDD group, controlling for BDI scores, age, medication status (currently taking antidepressants or not), gender, and ethnicity (categorical variables were dummy coded), also yielded a significant main effect of C957T, $F(2, 299) = 4.54$, $p = .029$, $\eta^2 = .029$, suggesting that the relation between depressive rumination and the C957T polymorphism in the depressed participants is not attributable to these variables.[1] In this ANCOVA, BDI scores, $F(1, 299) = 54.4$, $p < .0001$, $\eta^2 = .154$, and age, $F(1, 299) = 8.6$, $p = .004$, $\eta^2 = .028$, also predicted brooding; no other variables were significant.

Discussion

Investigators have found that difficulties with suppression and punishment learning are related to rumination (e.g., Joormann, 2010) and that 957C-allele homozygotes have more difficulties learning from punishment and suppressing irrelevant information than do individuals with one or two 957T alleles (e.g., Frank et al., 2009). In this context, we postulated that depressed individuals who are 957C-allele homozygotes would engage in more frequent rumination than would depressed individuals with one or two 957T alleles. Consistent with this prediction, we found that depressed 957C-allele homozygotes reported a higher tendency to engage in depressive rumination than did depressed individuals with one or two 957T alleles, even after controlling for symptom severity, ethnicity, age, gender, and medication status. We posit that suppression and punishment learning are the cognitive factors that mediate this relation. More specifically, depressed individuals who are 957C-allele homozygotes may ruminate more than do depressed individuals with one or two 957T alleles because they have more difficulty learning that their rumination leads to punishment and find it harder to suppress their rumination once they realize it is punishing. It is important to emphasize, however, that because we did not measure suppression or punishment learning in this study, we cannot conclude that differences in suppression and punishment learning are the cognitive mechanisms driving the relation between the *DRD2* gene and depressive rumination. Future research should examine this formulation more explicitly.

As we predicted, the effect of the C957T polymorphism on frequency of rumination was weaker in the never-depressed than in the depressed group. This finding was expected, given our assumption that punishment learning and suppression mediate the relation between the *DRD2* genotype and rumination, for two reasons. First, ruminative thinking leads to less punishment if individuals are not in a depressed mood. For example, investigators have found that rumination inductions lead to impaired problem solving, more negative mood, and increased negative thinking in depressed, but not in nondepressed,

[1] To further examine the potential effects of ethnicity, we conducted all of the analyses using only the data from the non-Hispanic Caucasian subsample and obtained comparable results in all analyses.

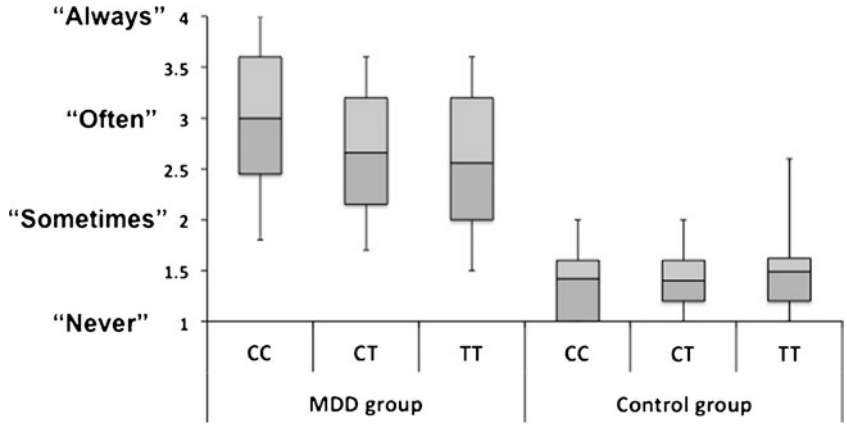

Fig. 1 A box plot of the frequency of rumination in participants between groups and across genotype. We used the 9th and 91st percentiles for the minimum and maximum values, respectively. The *y*-axis is the average score on the brooding subscale of the Ruminative Response Styles scale, ranging from *almost never* to *almost always*

individuals (see Nolen-Hoeksema et al., 2008). If rumination leads to less punishment in never-depressed individuals, their ability to learn from punishment is less likely to affect how frequently they ruminate. Thus, the C957T polymorphism may have a larger effect on the frequency of rumination in depressed than in never-depressed individuals, as we found, because rumination is more likely to be associated with punishment in depressed individuals.

Second, the C957T polymorphism may have had a larger effect in depressed individuals, not because of the presence of a depressed mood per se, but because of the high frequency of rumination that occurs with depressed mood. In the present study, depressed and never-depressed individuals reported very different frequencies of rumination. Approximately 90 % (278/317) of the never-depressed participants scored 2 or less on the rumination scale (2 indicates that participants *sometimes* ruminate), and about 50 % (152/317) had scores of 1.2 or less (1 indicates that participants *almost never* ruminate). In contrast, only 4 out of 317 never-depressed participants scored 2.8 or higher on the brooding subscale (3 indicates that participants *often* ruminate), as compared with half (159/317) of the depressed participants, who scored 2.8 or higher on the scale. If rumination occurs rarely and stops on its own, as it probably does in never-depressed individuals, individuals would have little need to actively exert suppression to stop that rumination. Moreover, low levels of rumination will be less likely to interfere with adaptive behaviors and, therefore, to lead to punishment. Thus, individual differences in the ability to exert suppression or to learn from punishment may have a greater impact on the frequency of rumination as the frequency of rumination increases. In this context, the C957T polymorphism may have had a larger effect on the frequency of rumination in depressed than in never-depressed individuals, because of the higher levels of rumination in depressed individuals.

It is not clear whether it was the presence of a depressed mood, the high frequency of rumination in depressed individuals, or both of these factors that was underling the effect of depression status had on the relation between the C957T polymorphism and rumination in the present study. If frequency of rumination is the central factor, we would expect the C957T polymorphism to be strongly related to rumination in individuals who report a high frequency of rumination, even if they are not depressed. Unfortunately, we cannot examine this possibility in the present study because very few never-depressed participants reported frequent rumination. Future studies that use more liberal exclusion criteria for the nondepressed group (e.g., that exclude participants for current depression, but not for a history of depression or of other psychopathology, as we did in the present study) may be able to determine whether depressed mood, high frequency of rumination, or both underlie the effect of depression status on the relation between rumination and the C957T polymorphism.

One of the most important implications of the present study is that because the C957T polymorphism of the *DRD2* gene affects DRD2 function (i.e., DRD2 availability and mRNA translation and stability; Duan et al., 2003; Hirvonen et al., 2005, 2009), our results suggest that DRD2 function influences frequency of rumination in depressed individuals. This finding is particularly noteworthy given that DRD2 are dopaminergic, indicating that dopamine might affect the frequency of rumination in depressed individuals. Clearly, more research is needed to confirm and elucidate the role of DRD2 and dopamine in rumination. The present results indicate, however, that it may be possible to target rumination pharmacologically with drugs that affect DRD2.

A major advantage of investigating the relation between rumination and the C957T polymorphism is that investigators have established how this polymorphism affects functioning at both the neural (molecular and circuit) and cognitive levels. On the basis of this work, we can identify a general cascade from genotype to cognitive functioning that could underlie rumination. As we noted earlier, the C957T polymorphism affects the functioning of DRD2 receptors, which are expressed predominantly in the indirect pathway of the BG (Gerfen, 2000). According to the go/no-go model of BG function (see Frank & Fossella, 2011; Maia &

Frank, 2011; O'Reilly & Frank, 2006), dopamine tonically stimulates DRD2, and, because DRD2 is coupled to inhibitory G-proteins, the activation of DRD2 will lead to tonic suppression of the indirect, or "no-go," pathway. Punishment, which is signaled by a temporary pause in dopamine firing, will lead to decreased activation of DRD2 and, thereby, to increased activation of the no-go pathway. According to the go/no-go model, activation of the no-go pathway will lead to suppression of cognitive actions (e.g., WM updating, motor selection) that are associated with punishment (i.e., a pause in dopamine firing), because the no-go pathway inhibits the thalamus, thereby blocking the relay of neural activity from posterior and ventral cortices (e.g., information in LTM/sensory cortex) through the thalamus to the prefrontal cortex, the neural locus of WM.

According to the no-go model, if the availability of DRD2 is reduced, as it is in 957C-allele homozygotes, individuals will learn less from the dip in dopamine that follows the punishment of an action. Because of this decreased learning from dopamine dips, future encounters with a previously punished action will lead to less deactivation of DRD2, resulting in less activation of the no-go pathway and, thereby, decreased suppression of those actions (Frank et al., 2009; Frank & Hutchison, 2009; Frank et al., 2007). We postulate that decreased learning in and activation of this no-go mechanism could affect the frequency of rumination in depressed individuals. Depressed individuals with low DRD2 availability may be less likely to learn that rumination leads to punishment; therefore, their no-go pathway may be less likely to facilitate the suppression of ruminative thoughts.

If this no-go model of rumination is correct, it suggests that factors other than the C957T polymorphism that also affect NoGo functioning could exacerbate rumination in depressed individuals. Moreover, given that the no-go pathway functions, along with the direct, or "go," pathway, as part of a gateway to WM, this model suggests that a faulty WM gateway underlies rumination in depressed individuals. Thus, this model could explain at a neural level why ruminators repetitively update negative, depressive thoughts into WM, despite the fact that those thoughts have adverse consequences. Researchers could profitably continue to examine this no-go model of rumination, investigating the association of rumination and no-go functioning using other methodologies, such as positron emission tomography or magnetic resonance spectroscopy.

We are aware that the results of candidate gene association studies do not always replicate (e.g., Risch et al., 2009). Although the present findings certainly should be replicated, there are important strengths of this study that we believe increase the likelihood of replication. First, we used a relatively large sample of 634 depressed and never-depressed individuals, increasing the reliability of the obtained results. Second, it is noteworthy that the association between rumination and the C957T polymorphism not only was significant, but also was in the predicted direction: Depressed 957C-allele homozygotes reported more maladaptive rumination than did depressed individuals with one or two 957T alleles. Third, this study was not exploratory but, instead, was motivated by the precise theoretical postulation that functioning of the no-go pathway affects the frequency of rumination in depressed individuals. As we described above, the C957T polymorphism is thought to affect the functioning of this no-go system.

Finally, although the relation between the C957T polymorphism and depressive rumination was significant, the effect size was not large. It is important to note, however, that in this study, we examined only one component (i.e., one gene) of the complex no-go pathway that we believe is involved in rumination. It is likely that other components (genetic and nongenetic) of the no-go pathway are also related to trait rumination; investigators may find a significant association between these other components and rumination even in nondepressed individuals (although we would predict a weaker relation than is the case in depressed individuals). The combined effect of these multiple components on rumination has the potential to be substantially larger.

In the present study, we found that depressed individuals who are homozygous for the 957C allele of the *DRD2* gene are more likely to ruminate than are depressed individuals with one or two 957T alleles. This finding suggests that DRD2 and dopamine affect the frequency of depressive rumination. We have postulated a "no-go" model of rumination to explain the association between rumination and *DRD2*, and we encourage researchers to examine this model more explicitly and systematically.

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