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The Catechol-*O*-Methyl Transferase Val[158]Met Polymorphism and Experience of Reward in the Flow of Daily Life

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Genetic moderation of experience of reward in response to environmental stimuli is relevant for the study of many psychiatric disorders. Experience of reward, however, is difficult to capture, as it involves small fluctuations in affect in response to small events in the flow of daily life. This study examined a momentary assessment reward phenotype in relation to the catechol-*O*-methyl transferase (COMT) Val[158]Met polymorphism. A total of 351 participants from a twin study participated in an Experience Sampling Method procedure to collect daily life experiences concerning events, event appraisals, and affect. Reward experience was operationalized, as the effect of event appraisal on positive affect (PA). Associations between COMT Val[158]Met genotype and event appraisal on the one hand and PA on the other were examined using multilevel random regression analysis. Ability to experience reward increased with the number of 'Met' alleles of the subject, and this differential effect of genotype was greater for events that were experienced as more pleasant. The effect size of genotypic moderation was quite large: subjects with the Val/Val genotype generated almost similar amounts of PA from a '*very* pleasant event' as Met/Met subjects did from a '*bit* pleasant event'. Genetic variation with functional impact on cortical dopamine tone has a strong influence on reward experience in the flow of daily life. Genetic moderation of ecological measures of reward experience is hypothesized to be of major relevance to the development of various behavioral disorders, including depression and addiction.

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INTRODUCTION

The G>A mutation that produces a valine-to-methionine (Val/Met) substitution within the catechol-*O*-methyl transferase (COMT) gene has been widely researched and associated with several behavioral disorder phenotypes, including mood disorders (Funke *et al*, 2005; Massat *et al*, 2005), schizophrenia (Caspi *et al*, 2005; Fan *et al*, 2005; Funke *et al*, 2005), and substance dependence (Vandenbergh *et al*, 1997; Redden *et al*, 2005; Beuten *et al*, 2006; Brody *et al*, 2006). However, results have been inconsistent. In the field of mood disorders, some studies show an increased risk for major depression and bipolar disorder in Val allele carriers (Funke *et al*, 2005; Massat *et al*, 2005). Other studies, however, did not find associations with mood disorder (Frisch *et al*, 1999; Henderson *et al*, 2000) and some found the Met allele to be risk-increasing (Ohara *et al*, 1998; Smolka *et al*, 2005; Szegedi *et al*, 2005). The same inconsistency in findings applies to studies concerning other behavioral disorder phenotypes. It has been suggested that one of the reasons for the inconclusive results is related to the substantial amount of problems inherent to any attempt to make a direct association between a genotype and a phenotype representing a complex behavioral disorder (Kendler, 2005). It has thus been argued that (i) the action of genes is likely modified by environmental exposures and (ii) the causal chain of action from a gene to developing a complex behavioral disorder is much too long (Kendler, 2005). Thus, a more productive way from genotype to disease development may be to not only incorporate gene-environment interactions (Caspi and Moffitt, 2006), but also decrease the distance in explanatory

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level. Thus, the level of explanation that can be related to gene action is more likely a basic biological or mental process, which may contribute itself to the development of disorder (Kendler, 2005).

It is hypothesized that a basic mental process related to COMT enzyme activity, early in the chain from genotype to phenotype, is the ability to experience reward. In the brain, the rewarding effects of, for example, food and drugs have been associated with the mesolimbic dopamine (DA) system (Nestler and Carlezon, 2006). Studies found that the pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NA), mediated by dopaminergic neuronal transmission, is implicated in the responses to natural (Kelley and Berridge, 2002) and unnatural (eg psychotropic drugs) (Wise, 1998) rewards. The orbitofrontal cortex, which has reciprocal links with the mesolimbic system, is important in hedonic processing and reward-related behaviors, and implicated in the conscious subjective experience of pleasure and reward (Galvan *et al*, 2005; Kringelbach, 2005). In addition, D2 receptor function has been associated with the personality dimension 'positive emotionality' (Depue *et al*, 1994). Animal studies show that the COMT enzyme, a catecholamine catabolizer, tightly regulates DA neurotransmission in both subcortical (VTA and NA) and prefrontal areas, and plays a major role in the interaction between these areas with respect to DA signalling (Bilder *et al*, 2004; Craddock *et al*, 2006). As the brain reward system depends on DA neurotransmission in mesolimbic and frontal areas, COMT enzyme activity is likely to impact on reward experience. In animals, it has also been shown that DA is able to exert effects at great diffusional distances in the prefrontal cortex (PFC), as this area has a low frequency of the DA transporter. Therefore, in the PFC, COMT enzyme activity has a significant impact on general levels of DA signaling (Bilder *et al*, 2004; Craddock *et al*, 2006; Meyer-Lindenberg *et al*, 2006). In humans, the PFC is the site where the conscious experience of rewarding effects likely takes place. Although human studies regarding COMT–DA interactions in the PFC are scarce, taken together, the literature suggests a prominent role for COMT in processes of reward.

The human COMT Val[158]Met polymorphism genotypes are associated with differential enzyme activity. Homozygosity for the Val allele yields a three- to four-fold increase in COMT activity relative to Met homozygotes, whereas heterozygote subjects have intermediate activity (Syvanen *et al*, 1997). It is expected that carrying the Val allele would result in lower prefrontal DA levels compared with the Met allele (Bilder *et al*, 2004; Craddock *et al*, 2006). It is therefore attractive to hypothesize that COMT Val[158]Met genotype will be associated with reward experience, in the direction of higher levels of reward with higher levels of Met loading.

The ability to experience rewarding effects of environmental events may affect the vulnerability for the development of several behavioral disorders (Chau *et al*, 2004), such as depression (Tremblay *et al*, 2005) or addiction (Reuter *et al*, 2005). Previous human studies on reward and depression focused on reward elicited by drugs (Tremblay *et al*, 2005), cognitive reward tasks (Cohen *et al*, 2005; Keedwell *et al*, 2005), or retrospective questionnaires (Hopko *et al*, 2003). However, these measures may have limited ecological validity with regard to reward experience in the flow of daily life. In the current study, a momentary assessment technique known as the Experience Sampling Method (ESM) (Delespaul, 1995; Myin-Germeys *et al*, 2001) was used to examine prospectively, in the flow of daily life, the ability to experience rewarding effects of the environment. Reward experience was operationalized as the effect of small events occurring in the flow of daily life on positive affect (PA). We hypothesized a COMT Val[158]Met genotype X event interaction in the association with PA, measured in the flow of daily life.

MATERIALS AND METHODS

Subjects

The study sample consisted of 621 participants aged 18–46 years who were taking part in an ongoing longitudinal, general population twin study on gene–environment interaction in affective disorders. Most participants (twins) were recruited from the East-Flanders Prospective Twin Survey. This population-based survey has prospectively recorded all multiple births in the province of East-Flanders since 1964 (Loos *et al*, 1998; Derom *et al*, 2002). Zygosity was determined through sequential analysis based on sex, fetal membranes, blood groups, and DNA fingerprints. The project was approved by the Local Ethics Committee and all participants gave written informed consent. Participants were white and of Belgian origin. The sample was female only given important sex differences in etiology and expression of common mental disorders (Fanous *et al*, 2002; Spauwen *et al*, 2003; Myin-Germeys *et al*, 2004; Ko *et al*, 2005).

Experience Sampling Method

ESM is a structured diary technique to assess subjects in their daily living environment, and has been extensively validated for the use of immediate effects of stressors on mood (Csikszentmihalyi and Larson, 1987; DeVries, 1992; Delespaul, 1995; Myin-Germeys *et al*, 2001). Subjects received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. The wristwatch was programmed to emit a signal ('beep') at an unpredictable moment in each of ten 90-min time blocks between 0730 and 2230, on 5 consecutive days. After each beep, subjects were asked to fill out the ESM self-assessment forms previously handed to them, collecting reports of thoughts, current context (activity, persons present, and location), appraisals of current situation and mood. All self-assessments were rated on seven-point Likert scales. Trained research assistants with ample experience in momentary assessment techniques explained the ESM procedure to the participants during an initial briefing session and a practice form was completed to confirm that subjects were able to understand the seven-point Likert scale. Subjects could call a telephone number in case they had questions or problems during the ESM sampling period. Subjects were instructed to complete their reports immediately after the beep, thus minimizing memory distortion, and to record the time at which they completed the form. In order to verify whether subjects had completed

the form within 15 min of the beep, the time at which subjects indicated they completed the report was compared with the actual time of the beep. All reports not filled in within 15 min after the beep were excluded from the analysis, as previous work (Delespaul, 1995) has shown that reports completed after this interval are less reliable and consequently less valid. In addition, subjects with less than 17 valid reports (out of 50) were excluded from the analysis, as previous work has shown that measures of individuals with less than 30% of completed reports are less reliable (Delespaul, 1995).

Measurements

Genotyping. Placental tissue for DNA analysis was available for 156 participants, blood samples for 14, and buccal cell samples for 208, using a sterile swab specifically designed for the collection of buccal cell samples for DNA testing (Omni Swabs; Whatman plc, Brentford, England).

Genomic DNA was extracted using QIAamp DNA Mini Kits (Qiagen, Venlo, The Netherlands) according the appropriate protocol for each sample type. COMT Val[158]Met genotype was determined by KBioscience (Hertz, UK) using their proprietary allelic discrimination assay (for details see http://www.kbioscience.co.uk).

For every monozygotic (MZ) twin in the sample with genotypic data, the same genotypic data were included for the co-twin, assuming that both twins had identical genotypes. In the analyses, the genotype was expressed as follows: 1 = 2 'Val' (high activity) alleles (HH); 2 = 1 'Val' and 1 'Met' (low activity) allele (HL); 3 = 2 'Met' alleles (LL). GenBank accession number for the COMT gene is NM_007310.

Reward experience in daily life. Appraisals of minor daily events and PA were collected at each beep within the ESM framework. Subjects were asked to report the most important event that happened between the current and the previous beep. This event was subsequently rated on a seven-point bipolar scale (from $-3 =$ *very unpleasant*, $0 =$ *neutral*, to $3 =$ *very pleasant*).

ESM PA was assessed at each beep with four mood adjectives (I feel 'cheerful', 'content', 'energetic', and 'enthusiastic') rated on seven-point Likert scales as described above. The mean of the four items formed the PA scale (Cronbach's alpha = 0.88 over the subject mean). The same was followed for negative affect, which was assessed with six mood adjectives (I feel 'insecure', 'lonely', 'anxious', 'low', 'guilty', and 'suspicious') and a Cronbach's alpha of 0.88 over the subject mean.

Only observations including events appraised as neutral (0—the reference category), a bit pleasant (1), pleasant (2), and very pleasant (3) were included in the analyses of reward experience in daily life, as the definition of reward does not include unpleasant events resulting in rewarding effects. Reward experience was operationalized as the effect of minor daily event appraisal on PA.

Analyses

ESM data have a hierarchical structure. Thus, multiple observations (level 1) were clustered within subjects (level 2), who were part of twin pairs (level 3). Multilevel analysis takes the variability associated with each level of nesting into account (Snijders and Bosker, 1999). The XTMIXED command in STATA 9.1 (Statacorp, 2006) was used to perform multilevel linear regression analyses.

First, it was examined whether higher appraisal of an event in terms of 'pleasantness' was associated with higher PA scores: '$PA_{ijk} = \text{constant} + \beta 1 \times \text{appraisal event}_{ijk} + \varepsilon_{ijk} + \mu_{jk} + v_k$' (the β is the fixed regression coefficient; the error terms reflect residual variation at level of observations (ε_{ijk}), individuals (μ_{jk}), and twins (v_k)). Second, the degree of dose–response between event appraisal (0–3) and PA was examined by creating three event-dummies. Third, in order to examine whether mediating effects of COMT confounded the hypothesized moderating effect, main effects of COMT genotype on event appraisal and PA were examined. Fourth, indirect and direct genetic effects on PA were examined. Indirect effects were examined using within-pair MZ and DZ associations. Furthermore, in order to examine whether variation in COMT (HH, HL, LL) genotype impacted on reward experience in daily life, we examined the interaction between COMT and event appraisal in the association with PA: '$PA_{ijk} = \text{constant} + \beta 1 \times \text{appraisal event}_{ijk} + \beta 2 \times \text{COMT}_{jk} + \beta 3 \times \text{appraisal event} \times \text{COMT}_{ijk} + \varepsilon_{ijk} + \mu_{jk} + v_k$'. Effect sizes of the interactions between the three COMT variants on the one hand and event appraisals on the other were calculated by applying and testing the appropriate linear combinations using the STATA LINCOM command. Main effects and interactions were assessed by Wald test (Clayton and Hill, 1993).

Analyses were controlled for negative affect, as negative affect and PA correlate with each other ($r = -0.31$). As only observations with event ratings from 'neutral' to 'very pleasant' were included in the analyses, analyses were controlled for the number of observations each person contributed to the analyses, in order to take into account possible systematic differences in event appraisal through, for example, personality differences.

RESULTS

Subject Characteristics

Out of 621 subjects, 129 refused genotyping and for the 492 consenting subjects, samples suitable for DNA analysis were available for 412 (378 + 34, as for 34 MZ subjects DNA was indirectly available through measurement in the twin sister), of which 393 yielded valid COMT genotype measurements (including genotype derived from MZ twin sister). Of the 393 subjects, six were not included due to ambiguity concerning rank or zygosity and another 36 had incomplete ESM measurements. This resulted in a sample of 351 subjects, of which 327 were female members of twin pairs (189 subjects were members of MZ twin pairs, 137 subjects were members of dizygotic twin pairs and one subject was of unknown zygosity) and 24 were non-twin sisters.

Mean age of the twins was 27 years (SD: 8.1 years). Sixty-five percent had a college or university degree, 33% completed secondary education and 2% had primary education only. The majority was currently employed (60% employed, 35% student, 2% unemployed, and 4%

homemaker). The frequencies of the three COMT genotypes were: HH, 23.6%; HL, 54.7%, and LL, 21.7%, comparable with previous reported frequencies in similar samples (Olsson *et al*, 2005; Redden *et al*, 2005) and in Hardy–Weinberg equilibrium ($\chi^2 = 0.81$; df = 1; $p = 0.4$).

Reward Experience in Daily Life

Event appraisals included in the analyses were those with appraisals ranging from 'neutral' (0) to 'very pleasant' (3). The mean number of events per subject was 29.9 (SD: 10.3). Mean appraisal of events was 1.50 (SD: 1.16) and mean PA was 3.61 (SD: 0.98).

Event appraisal was significantly associated with PA scores (B = 0.10, $p < 0.001$). A dose–response relationship was apparent in that the more pleasant the event, the greater the effect size (reward experience) of event on PA score (Figure 1).

COMT Genotype Variation and Reward Experience

The main effect of COMT Val[158]Met genotype variation on appraisal of event was neither large nor significant (B = 0.01, $p = 0.2$). The same was true for the main effect of COMT Val[158]Met on PA score (B = −0.007, $p = 0.4$).

A significant association (B = 0.35, $p < 0.001$) was apparent between PA score of twin 1 and PA score of twin 2, indicating genetic and/or environmental contribution to PA. Moderation of this association by zygosity (testing the degree to which MZ twins are more similar than DZ twins, as an indication of the contribution of genetic factors) depended on COMT Val[158]Met genotype, as expected in the case of gene–environment interaction (Kendler, 1995). Thus, evidence for genetic effects was strongest in the COMT Val[158]Met met/met group: rMZ = 0.45 ($p < 0.001$), rDZ = 0.04 ($p = 0.18$), p interaction = 0.09; compared with rMZ = 0.22 ($p < 0.001$) and rDZ = 0.30 ($p < 0.001$), p interaction = 0.9, for the val/val group.

The association between COMT genotype variation and reward experience in daily life was examined by calculating the interaction effect between COMT and event appraisal in the association with PA. This interaction was significant: subjects with more 'Met' (L) alleles had a dose-dependent increase in the effect of event appraisal on PA (B = 0.038, $p = 0.027$ for HL and B = 0.070, $p = 0.001$ for LL in comparison with HH). Stratified effect sizes calculated with the LINCOM procedure are displayed in Figure 2. The three lines represent reward experience (the effects sizes of event appraisal on PA) stratified by COMT genotype. As indicated in the figure, increased reward experience associated with increased number of COMT 'Met' alleles was apparent at all levels of event appraisal. In addition, the pattern of effect sizes and Wald tests (Table 1) indicate that the more pleasant the event, the stronger the differential effect of COMT genotype with respect to reward experience.

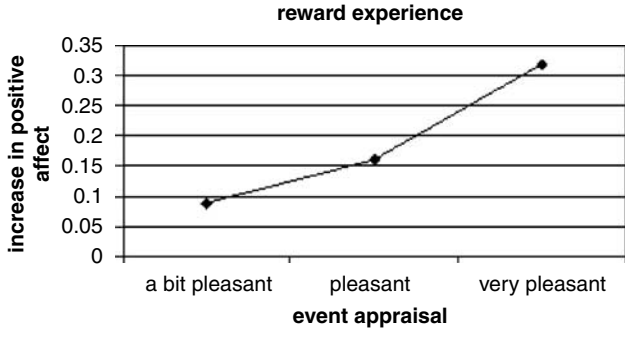

Figure 1 Dose–response relationship in the association between event appraisal and PA, indicating increased reward experience for events appraised as more pleasant.

DISCUSSION

Results show that variation in COMT Val[158]Met genotype moderates the ability to experience reward from events that happen in the flow of daily life. Ability to experience reward increases with the number of 'Met' alleles of the subject, and

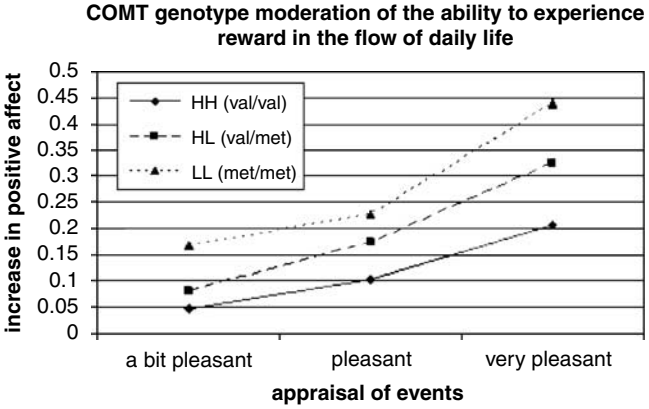

Figure 2 Reward experience on the continuum of event appraisal stratified by COMT genotype (event reference category is 'neutral').

Table 1 Effect Sizes and Wald Tests Comparing the HL and LL COMT Genotype with the HH Genotype, Stratified Per Level of Event Appraisal

Event appraisal compared to 'neutral'	COMT genotype	Effect size[a]	χ^2	*p*-value
A bit pleasant	HH	0.049		
	HL	0.082	0.36	0.5
	LL	0.168	3.04	0.08
Pleasant	HH	0.105		
	HL	0.175	1.76	0.2
	LL	0.227	3.67	0.05
Very pleasant	HH	0.209		
	HL	0.325	4.53	0.03
	LL	0.437	11.75	<0.001

[a]The third column shows the effect sizes of event appraisal on positive affect (PA), stratified for COMT genotype, using 'neutral' events as reference category. Wald tests are performed to test difference in effect size between the HL (Val/Met) and LL (Met/Met) COMT genotype compared to the HH (Val/Val) genotype, within each level of event appraisal.

this differential effect of genotype was greater for events that were experienced as more pleasant. The effect size of genotypic moderation was quite large: as can be read from Figure 2, subjects with the Val/Val genotype generated almost similar amounts of PA from a '*very* pleasant event' as Met/Met subjects already did from a '*bit* pleasant event'. Thus, COMT Val[158]Met genotype strongly moderates experience of reward, even at the level of *small* daily life positive experiences.

Implications for Behavioral Disorders

Individual variation in the ability to experience reward may have great relevance for the development of behavioral disorders. One of the core emotions of major depression, for example, is anhedonia, or the inability to experience pleasure from events that are normally experienced as pleasant. Decreased ability to experience reward, therefore, can be hypothesized as a vulnerability trait to develop depression. Studies have demonstrated that depressed subjects show altered biological and cognitive responses towards rewarding stimuli (Hughes *et al*, 1985; Tremblay *et al*, 2002, 2005). However, only few studies have been conducted in this area. Future research should aim to examine longitudinally whether reward deficiency is predictive for the development of depression.

A substantial amount of research has focused on addiction and substance abuse in relation to altered reward processing and the DA system. Decreased activation of the reward system has been reported in addicted subjects (Reuter *et al*, 2005) and there is evidence for a pre-existing reward deficiency rather than a drug-induced deficiency alone: rats bred for alcohol preference but *without* alcohol exposure show a deficit in the mesolimbic pathway (Zhou *et al*, 1995; Chau *et al*, 2004). In addition, addiction vulnerability is influenced by genetic factors. In accordance with the current results, the 'Val' variant of the COMT polymorphism, associated with low resting DA tone (but higher subcortical phasic DA responses) (Bilder *et al*, 2004) is associated with nicotine dependence and polysubstance abuse (Vandenbergh *et al*, 1997; Beuten *et al*, 2006; Brody *et al*, 2006).

The ability to experience rewarding effects is directly relevant to the amount of positive emotions a person may generate from minor events in daily life. Studies show that the experience of positive emotions is highly protective against the development of stress-induced mental and physical symptoms (Fredrickson and Levenson, 1998; Fredrickson, 2001; Strand *et al*, 2006; Wichers *et al*, 2007). Therefore, the ability to experience reward may be relevant to mental health in a much broader context than depression and addiction. Although reward experience is, in part, genetically influenced, the search for methods to manipulate and increase this ability in humans may be of great importance for a wide range of psychosocial and stress-related problems in the normal population.

Limitations

Some methodological limitations are apparent. First, it has been suggested that problems may arise in the ESM procedure, as it depends on the compliance of subjects (Kudielka *et al*, 2003; Broderick *et al*, 2004). In particular fixed time, sampling protocols may be problematic and can bias results. However, this report did not use a fixed-time sampling frame, and our ESM procedure was validated in a previous report. Thus, the same sample as described in the current analysis (Jacobs *et al*, 2005) was instructed to take, during the ESM procedure, saliva samples at each of the 10 unpredictable moments during the 5 consecutive days. Subjects recorded collection times, not being aware of that compliance with the sampling protocol was being investigated by means of electronic monitoring devices. Results showed that compliance was high (over 90%) and inclusion of the inaccurately timed samples did not distort the data (Jacobs *et al*, 2005). Therefore, results from the ESM procedure in this report can be considered valid.

Second, the present study was longitudinal but essentially assessed multiple cross-sectional relationships at each ESM moment, which made it impossible to establish causal relationships. Therefore, it is impossible to determine whether subjective appraisal of events influences mood, or whether mood influences the appraisals of events. However, either explanation bears clinical relevance, and the interpretation that appraisal of events contributes at least in part to measures of mood has high face validity.

The fact that our study included only female subjects is a strength as well as a limitation. Previous studies found sex-specific effects for COMT polymorphisms (Shifman *et al*, 2002; Handoko *et al*, 2005). The current study, therefore, represents a large sample unconfounded by sex. The logical disadvantage is that the results are not necessarily generalizable to the male population.

Finally, the COMT Val[158]Met polymorphism is in linkage disequilibrium and shows interaction effects with other COMT polymorphisms (Handoko *et al*, 2005; Stein *et al*, 2005; Beuten *et al*, 2006). In this study, only information for the Val/Met polymorphism was available and not for any additional genetic variation within the COMT gene. However, Meyer-Lindenberg *et al* (2006) argue that the findings implicating the COMT Val[158]Met polymorphism in prefrontal function are consistent, and that the importance of including additional information on genetic variability in COMT may be more relevant for studies examining associations with schizophrenia rather than prefrontal function, as evidence supporting the association between COMT Val[158]Met and schizophrenia, contrary to evidence implicating prefrontal function, is inconclusive. The hypothesis in this paper is directly related to the effect of COMT activity in regulating prefrontal DA function and thus, if correct, dose–response associations with the single polymorphism should be detectable, which was confirmed in the results. However, insufficient knowledge is available in literature concerning genetic interactions. Therefore, inclusion of haplotype measurements or other interacting COMT polymorphisms in the study may further fine tune the association between the genetic regulation of COMT enzyme activity and reward experience.

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CONFLICT OF INTEREST

None.

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