Candidate genes for novelty-seeking: a meta-analysis of association studies of *DRD4* exon III and *COMT* Val158Met

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Objective **Two widely studied genetic polymorphisms in the dopaminergic system [*DRD4* exon III variable number of tandem repeat (VNTR) and *COMT* Val158Met] have been reported to be associated with novelty-seeking, but the results have been highly inconsistent. Therefore, a meta-analysis of the associations between these two polymorphisms and novelty-seeking was conducted.**

Participants and methods **For *DRD4*, 24 studies comprising 27 samples and including 4933 participants were selected. Genotype grouping, sex, mean age, ethnicity, and sample characteristics were examined as moderators. For *COMT*, nine studies comprising 13 samples and including 2633 participants were selected. Sex, mean age, ethnicity, and sample characteristics were included as moderators. We also tested for possible publication bias.**

Results **The significant association between the *DRD4* polymorphism and novelty-seeking was supported, but no association was found between the *COMT* polymorphism and novelty-seeking. In addition, our findings revealed that sex and age both directly moderate the relationship between *DRD4* and novelty-seeking. Meanwhile, ethnicity can interact with age, sex, and genotype grouping, and age and sex can interact with each other, to moderate the association between the *DRD4* exon III VNTR polymorphism and novelty-seeking.**

Conclusion **Our results provide evidence of association between the *DRD4* exon III VNTR polymorphism and novelty-seeking, which is inconsistent with the results of previous meta-analysis. Furthermore, several direct and indirect moderators are also identified to explain contradictory results in the existing literature. However, our results regarding *COMT* are consistent with those of previous meta-analysis. *Psychiatr Genet* 28:97–109**

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Keywords: ***COMT*** **Val158Met,** ***DRD4*** **exon III VNTR, meta-analysis, novelty-seeking**

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Introduction

Novelty-seeking refers to the tendency of humans and animals to explore unfamiliar stimuli and environments (Reed *et al.*, 1996) and is one of the three heritable dimensions assessed by the Tridimensional Personality Questionnaire (TPQ) (Cloninger *et al.*, 1991). Twin studies have estimated a relatively substantial heritability in novelty-seeking of between 30 and 40% (Stallings *et al.*, 1996). Recently, researchers have linked variation in genes in the dopaminergic system to individual differences in novelty-seeking (Bunzeck *et al.*, 2013). *DRD4* exon III variable number of tandem repeat (VNTR) and *COMT* Val158Met are the two most widely studied polymorphisms related to novelty-seeking. However, until now, empirical findings on their associations with novelty-seeking have been mixed. Therefore, the present study sought to examine the relationship between these two polymorphisms and novelty-seeking by conducting a systematic meta-analysis.

DRD4 exon III VNTR

The *DRD4* gene is located on chromosome 11p5.5. The *DRD4* exon III VNTR polymorphism is a 48-bp VNTR that codes for 16 amino acids in exon III, ranging from two to 11 copies. The most common polymorphism is the four-repeat (4r) allele found in Caucasians (Vallone *et al.*, 2000). Compared with 4r allele, cAMP formation, intracellular response to dopamine, and affinity of DRD4 to antagonists *in vitro* are all reduced in the presence of the seven-repeat (7r) allele (Oak *et al.*, 2000). In previous research, many association studies have found that the 7r allele is associated with higher novelty-seeking scores in young and healthy populations (Strobel *et al.*, 1999), heavily drinking college students (Ray *et al.*, 2009), and risky adolescents (Laucht *et al.*, 2007). This may be due to the reduction in sensitivity to dopamine and the increase in cravings for stimulation. However, in the existing literature, there are some inconsistent findings. For example, 7r was found to be associated with lower novelty-seeking in Finnish alcoholic offenders (Malhotra *et al.*, 1996), European American females (Gelernter *et al.*, 1997), and African American substance abusers (Gelernter *et al.*, 1997).

Furthermore, other studies have adopted a different method of analysis by grouping genotypes into 'short'

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Table 1 Description of studies and samples used in the meta-analysis of the association between *DRD4* exon III variable number of tandem repeat and novelty-seeking

							7− (s)			7+ (l)			Moderator coding				
	Measure	Country	Ethnicity	Sample size (sex)	Age (mean ± SD) (range)	Sample	Mean	SD	*n*	Mean	SD	*n*	7/l	Sex	Mean age	Ethnicity	Sample
Ebstein *et al.* (1996)	TPQ	Israeli	90 AJ, 25 SJ, 5 mixed AJ/SJ, 1 Ar, 1 Dr, 2 J	124 (44.4, f)	29.8 ± 8.9	Normal volunteer from student and staff at Ben-Gurion University and Beersheva Mental Health Center	15.45	4.47	90	17.94	6.06	34	1	1	1	1	1
Malhotra *et al.* (1996)	TPQ	Finland	Finnish	193	–	Normal control participants	18.13	4.73	133	17.55	4.57	60	1	–	1	1	1
Ebstein and Belmaker (1997)[a]	TPQ	Israeli	67 J, 27 nA	94 (47.9)	25.9 ± 3.8 (18–40)	Medical students and staff from Hadassah-Hebrew University Hospital and Medical School (Jerusalem)	16.45	5.2	64	17.83	6.35	30	1	1	1	1	1
Ebstein and Belmaker (1997)[b]						Expanded cohort	15.87	4.84	154	17.89	6.16	64	1	1	1	1	1
Gelernter *et al.* (1997)	TCI/TPQ	USA	65.7% EA, 34.3% AfA	341 (40.2, f)	35.4 ± 9.8	Substance-dependent participant, PD participant, controls	20.4	6.5	54	18.5	6.2	95	1	1	1	1	0
Ono *et al.* (1997)	TCI/TPQ	Japan	Japanese	153 (100, f)	18.7 ± 1.0	Student in a nursing junior college	21.4	5.8	134	23.13	5.62	19	0	2	0	0	1
Sanders *et al.* (1997)	TPQ	Germany	–	92 (0, f)	41.9 ± 9.4	Alcoholics	16.51	5.35	63	17.07	4.84	29	0	0	1	1	0
Noble *et al.* (1998)	TPQ	USA	Caucasian	119 (0, f)	12.1 ± 1.2	Elementary and junior high school	16.55	4.61	74	18.28	4.62	45	1	0	0	1	1
Pogue-Geile *et al.* (1998)	TPQ	USA	97% W, 2% AfA, 1% AsA	281 (56, f)	21.6 ± 2.9 (18–27)	Healthy same sex twins	16.98	4.72	179	17.15	5.65	102	1	1	0	1	1
Sullivan *et al.* (1998)[a]	TCI	New Zealand	New Zealanders	86 (60.1, f)	32 ± 11	Depression clinical trial	15.7	5.1	53	16	6	33	1	1	1	1	0
Sullivan *et al.* (1998)[b]				181 (50.3, f)	39.7 ± 14.1	Multiplex Alcoholic Pedigrees	15.7	5.3	99	16.4	5.5	82	1	1	1	1	0
Bau *et al.* (1999)	TPQ	Brazil	Caucasian	110 (0, f)	41 (20–63)	Alcoholics	15.54	4.41	72	16.16	4.44	38	1	0	1	1	0
Strobel *et al.* (1999)	TPQ	German	92% G	136 (64.7)	23.6 ± 3.9	Healthy student and staff from university	17.16	5.58	92	20.59	5.35	44	1	1	0	1	1
Tomitaka *et al.* (1999)	TCI	Japan	Japanese	69 (100, f)	25 ± 2.4	Medical student, hospital resident	21.82	5.42	56	25.85	3.78	13	l	2	1	0	1
Benjamin *et al.* (2000)	TPQ	Israeli	–	455 (60, f)	26.95 ± 10.4	High school, villages, kibbutz members, university students and staff	16.14	4.61	197	15.79	4.94	167	1	1	1	1	1
Gebhardt *et al.* (2000)	TCI	Austria	Caucasian	109 (71.6, f)	32.47 ± 7.44	Healthy normal volunteers	17.52	5.22	91	16.13	5.43	15	1	1	1	1	1
Herbst *et al.* (2000)	TCI	USA	83.5% W, 13.1% AA	587 (45.3, f)	m: 62.1 ± 15.5 (21–94); f: 55.4 ± 15.5 (20–93)	Healthy volunteer	16.6	5.6	367	16.5	6.3	220	1	1	1	1	1
Swift *et al.* (2000)	TPQ	Ireland	Irish	47	20 s	College student	16.66	5.99	35	17.83	4.65	12	0	–	0	1	1
Strobel *et al.* (2002)	TPQ	Germany	German	276 (74.3, f)	21.9 ± 3.9 (18–41)	Healthy volunteer	17.2	5.43	183	17.97	5.21	93	1	1	0	1	1
Lee *et al.* (2003)[c]	TCI	Korea	Korean	173 (100, f)	13.87 ± 0.3	Junior high school student	21.3	6.5	154	24.6	6.1	19	0	2	0	0	1

Lee *et al.* (2003)[d]	TCI	Korea	Korean	101 (100, f)	13.94 ± 0.33	–		20.97	6.71	88	23.46	7.5	13	0	2	0	0	1
Strobel *et al.* (2003)						Data same as in Strobel *et al.* (2002)												
Dan *et al.* (2004)	TPQ	Israel	–	81 (100, f)	–	Fibromyalgia patient		12.72	3.49	60	14.57	3.26	21	1	2	–	1	0
Tsai *et al.* (2004)	TPQ	Chinese	Han	120 (100, f)	19–21	Healthy nursing student		18.2	4.9	111	16.1	3.9	9	0	2	0	0	1
Becker *et al.* (2005)[f]	JTCI	Germany	Primarily Caucasian	144 (0, f)	15	High risk community sample		18.4	5.6	83	21.6	6.4	61	1	0	0	1	0
Becker *et al.* (2005)[g]	–	–	–	159 (100, f)	–	–		20.5	6.9	96	20.8	6.3	63	1	2	0	1	0
Kim *et al.* (2006)	TCI	Korea	Korean	214 (52.3, f)	27.5 ± 6.13	Nurses, students, volunteers		17.98	7.18	205	20.00	8.85	9	0	1	1	0	1
Laucht *et al.* (2007)						Data same as in Becker *et al.* (2005)												
Tsuchimine *et al.* (2009)	TCI	Japan	Japanese	616 (45.1, f)	28 ± 9.8 (18–69)	Healthy medical school student, medical staff		21.7	5.1	510	21.6	4.8	46	0	1	1	0	1

's' stands for 'short' allele (two to five repeats) ; 'l' stands for at least one 'long' allele carrier.
In sample size column, numbers in parentheses is percentage of female participants, 'f' stands for female.
Superscripts a and b are two samples within one study; c and d are two papers; f and g are male and female sample respectively within one study.
Moderator coding. Genotype grouping: 7r absence/presence coded as 1, l/s allele coded as 0. Sex:All-male sample coded as 0; mixed sample coded as 1; all-female sample coded as 2. Mean age: above 25 years coded as 1; below 25 years coded as 0. Ethnicity: primarily Caucasian coded as 1; Asian coded as 0. Sample: normal and healthy people coded as 1; abnormal coded as 0.
AfA, African American; AJ, Ashkenazi Jews; Al, Alaskan; Ar, Arab; AsA, Asian American; AZN, Asian; BL, Black; Dr, Druze; EA, European American; G, German; H, Hispanic; J, Jews; L, Latino; NA, Native American; nA, non-Ashkenazi; PD, Personality Disorder; PI, Pacific Islander; SJ, Sephardic Jews; W, White; WNH, White non-Hispanic.

(four or fewer repeats) versus 'long' (five or more repeats) alleles, though findings remain inconsistent. For instance, while Swift *et al.* (2000) and Lee *et al.* (2003a) found that long repeats were related to novelty-seeking, additional studies have reported no association between the polymorphism and novelty-seeking (Kim *et al.*, 2006; Tsuchimine *et al.*, 2009).

Among the limited meta-analyses in the existing literature, Schinka *et al.* (2002) reported that a small positive effect was found for long alleles, but other meta-analyses have failed to identify any significance (Munafò *et al.*, 2003, 2008). However, these latter studies, published in 2002 and 2003, only included empirical studies conducted before 2002. Moreover, Munafo *et al.* (2003) only reviewed studies with samples from healthy adults and included multiple personality traits scaled by the Neuroticism, Extraversion, Openness Personality Inventory; Tridimensional Personality Questionnaire (TPQ); Temperament and Character Inventory (TCI); Eysenck Personality Questionnaire-Revised; Sensation-Seeking Scale; and Karolinska Scales of Personality. Similarly, Munafò *et al.* (2008) also examined all approach-related personality traits with not only TCI/TPQ, but also Neuroticism, Extraversion, Openness and Karolinska Scales of Personality. In the present study, we included studies published after 2002, tested potential moderators, and focused only on novelty-seeking as measured by TCI/TPQ.

COMT Val158Met

The *COMT* gene is located on chromosome 22q11.1–q11.2 and encodes a protein that catalyzes the transfer of a methyl group from *S*-adenosylmethionine. It plays an important role in the inactivation of dopamine and thus has an impact on dopamine levels in the prefrontal cortex. The most extensively investigated single nucleotide polymorphism (rs4680) in the *COMT* gene is a G-to-A transition at codon 158, which leads to a Val-to-Met substitution (Val158Met), with the Met allele showing a quarter reduction in enzyme activity and higher dopamine levels in the prefrontal area compared with the Val allele (Lachman *et al.*, 1996). The two alleles (Val and Met) are co-dominant (Lotta *et al.*, 1995).

The Val/Val genotype has been correlated with higher novelty-seeking compared with the Val/Met or Met/Met genotypes (Reuter *et al.*, 2006). However, there have been studies that have returned the opposite results, observing higher novelty-seeking in those with the Met/Met genotype compared with Val carriers (Golimbet *et al.*, 2007). This may be because carriers of the Met allele show increased levels of 'tonic' dopamine release but decreased levels of phasic dopamine, and thus tend to seek high levels of additional stimulation (Bilder *et al.*, 2004; Reuter *et al.*, 2006). The characteristics of the samples used could also be a source of contradictory results. Moreover, there have been studies that have failed to identify any significant association between the Val allele and novelty-seeking, for example, in depressed patients (Light *et al.*, 2007), Caucasian or American Indian community samples (Enoch *et al.*, 2003), and young Korean

Table 2 Description of studies and samples used in the meta-analysis of the association between *COMT* Val158Met and novelty-seeking

							Met absence			Met presence			Moderator coding			
	Measure	Country	Ethnicity	Sample size (sex)	Age (mean ± SD) (range)	Sample	Mean	SD	n	Mean	SD	n	Sex	Mean age	Ethnicity	Sample
Benjamin *et al.* (2000)	TPQ	Israeli	–	455 (60, f)	26.95 ± 10.4	High school, villages, Kibbutz members, university students and staff	16.44	4.55	137	15.82	4.76	317	1	0	1	1
Tsai *et al.* (2004)	TPQ	China(Taiwan)	Han	120 (100, f)	19–21	Nursing student	19	4.6	71	16.52	4.31	49	2	0	0	1
Kim *et al.* (2006)[a]	TCI	Korea	Korean	138 (0, f)	28.1 ± 5.1	Nurses, students and volunteers	19.1	6.3	74	17.68	5.39	64	0	0	0	1
Kim *et al.* (2006)[b]				148 (100, f)	28.6 ± 6.2		17.3	5.4	76	18.05	5.39	72	2	0	0	1
Golimbet *et al.* (2007)	TCI	Russia	Russian	130 (56.9, f)[c]	32.2 ± 12.9	Mentally healthy people	9.4	4.3	18	9.8	3.23	49	1	1	1	1
Hashimoto *et al.* (2007)	TCI	Japan	Japanese	139 (66.2, f)	36.3 ± 12.1	Unrelated healthy participants	21.5	3.9	77	21.7	4.82	62	1	1	0	1
Ishii *et al.* (2007)	TCI	Japan	Japanese	478 (48.5, f)	29.3(18–60)	Unrelated staff and medical students at 5 hospitals	21.6	4.9	251	21.98	5.22	227	1	0	0	1
Light *et al.* (2007)[d,g]	TCI	New Zealand	142 Caucasian, 3 M, 1 AZN	146 (60, f)	31.7 ± 11.4 (above 18)	Depressed patient sample 1	51.8	13.61	38	51.51	17.14	108	1	1	1	0
Light *et al.* (2007)[e,g]			127 Caucasian, 7 M, 8 AZN, 1PI, 3 others	146 (72, f)	35.0 ± 9.8	Depressed patient sample 2	47.41	15.72	30	47.9	14.98	116	2	1	1	0
Demetrovics *et al.* (2010)[d]	TCI	Hungary	Caucasian	117 (30, f)	27.4 ± 3.7	Heroin-dependent patients;	25.1	6.2	35	25.61	5.92	82	0	0	1	0
Demetrovics *et al.* (2010)[e]				124 (73.4, f)		Control	20.9	6.2	32	21.45	5.9	92	2	0	1	1
Chen *et al.* (2011)[a]	TCI	China	Chinese	250 (0, f)	20.5 ± 1	Healthy Chinese college students	99.03	11.41	148	102.60	13.05	102	0	0	0	1
Chen *et al.* (2011)[b]				306 (100, f)			103.83	12.33	162	101.83	12.85	144	2	0	0	1

Superscripts a and b are male and female sample respectively within one study; c: full sample; d and e are two samples within in one study; data in g study was grouped and reported in Val presence/absence.
In sample size column, numbers in parentheses is percentage of female participants, 'f' stands for female.
Moderator coding. Sex: Percentage of female participants below 30% coded as 0; above 70% coded as 2; between 30 and 70% coded as 1. Mean age: above 30 years coded as 1; below 30 years coded as 0. Ethnicity: Caucasian coded as 1; Asian coded as 0. Sample: normal people coded as 1; abnormal coded as 0.
AZN, Asian; M, Maori; PI, Pacific Islander.

Table 3 Allele frequency of samples from studies included in the *DRD4* meta-analysis

	Country	Normal sample (Y/N)	2r	3r	4r	5r	6r	7r	8r
Malhotra *et al.* (1996)	Finland	Y	7.4	6.2	66.7	2.3	0.5	16.5	0.4
Gelernter *et al.* (1997)	USA	N	8.6	3.7	65.5	1.2	0.9	19.2	0.9
			5.6	0.4	64.1	4.3	0.9	20.9	3.4
Ono *et al.* (1997)	Japan	Y	15.9	NA	79.7	NA	1.3	Almost 0	–
Sanders *et al.* (1997)	Germany	N	10.3	4.6	65.9	1.0	0.2	16.9	0.8
			7.1	3.3	70.1	3.3	0.5	15.2	0.5
Noble *et al.* (1998)	USA	Y	8.4	2.9	66.4	12.6	0.4	19.7	0.8
Pogue-Geile *et al.* (1998)	USA	Y	7	2	69	1	–	20	1
Sullivan *et al.* (1998)[c]	New Zealand	N	NA	NA	60.8	NA	NA	22.8	NA
Sullivan *et al.* (1998)[d]	New Zealand	N	NA	NA	59.6	NA	NA	25.1	NA
Bau *et al.* (1999)	Brazil	N	10.9	3.2	65.9	0.4	0.9	18.6	–
Strobel *et al.* (1999)	Germany	Y	11.8	1.8	63.9	0.4	1.1	19.5	1.1
Tomitaka *et al.* (1999)	Japan	Y	13.8	0.7	76.1	6.5	0.7	2.2	–
Gebhardt *et al.* (2000)	Austria	Y	10.39	8.99	70.63	0.49	0.49	8.52	0.49
Herbst *et al.* (2000)	USA	Y	8.9	3.7	64.3	1.1	0.3	20.4	1.1
Swift *et al.* (2000)	Ireland	Y	9.6	6.4	70.2	–	1.1	10.7	2.1
Lee *et al.* (2003)	Korea	Y	10.49	1.44	82.3	0.62	3.91	1.23	–
Strobel *et al.* (2003)	Germany	Y	7.3	4.3	66.5	0.9	0.4	19.1	1.3
Dan *et al.* (2004)	Israeli	N	10.5	1.9	69.1	1.9	1.2	15.4	–
Tsai *et al.* (2004)	China	Y	21.6	NA	73.8	NA	NA	NA	–
Kim *et al.* (2006)	Korea	Y	9.8	–	88.1	1.4	0.2	0.5	–
Tsuchimine *et al.* (2009)	Japan	Y	12.0	1.7	73.8	8.6	–	3.8	–

9r and 10r are very rare and so forth not shown in this table.'–' stands for no presence in the sample. We only included the studies that report allele frequency information. N, no, NA, the allele is present in the sample but the data is not available; Y, yes.

Table 4 Allele frequency of samples from studies included in the *COMT* meta-analysis

	Country	Normal sample (Y/N)	Val	Met	Val/Val	Val/Met	Met/Met
Benjamin *et al.* (2000)	Israeli	Y	55.6	44.4	30.2	50.7	19.1
Tsai *et al.* (2004)	China (Taiwan)	Y	77.1	22.9	59.2	35.8	5
Kim *et al.* (2006)	Korea	Y	71.3	28.7	52.4	37.8	9.8
Golimbet *et al.* (2007)	Russia	Y	51.9	48.1	26.2	51.5	22.3
Hashimoto *et al.* (2007)	Japan	Y	71.6	28.4	55.4	32.4	12.2
Ishii *et al.* (2007)	Japan	Y	72.3	27.7	52.5	39.5	8
Light *et al.* (2007)	New Zealand	N	51	49	28	46	26
		N	54	46	28.5	51	20.5
Demetrovics *et al.* (2010)	Hungary	N	53.8	46.2	29.9	47.9	22.2
		Y	50	50	26.2	49.2	26.2
Chen *et al.* (2011)	China	Y	74.7	25.3	55.8	37.8	6.5

participants (Kim *et al.*, 2006). In addition, in a previous study, it was reported that the association between the *COMT* polymorphism and novelty-seeking could only be observed in females, not in males (Kim *et al.*, 2006). These sex-specific results have been widely reported (Harrison and Tunbridge, 2008), implying that sex may be a potential moderator. Until now, there has been only one meta-analysis of the relationship between the COMT polymorphism and novelty-seeking that reported a nonsignificant result (Calati *et al.*, 2011). Hence, in this study, we aimed to contribute to the field by performing a meta-analysis of this relationship and examining potential moderators.

The current study

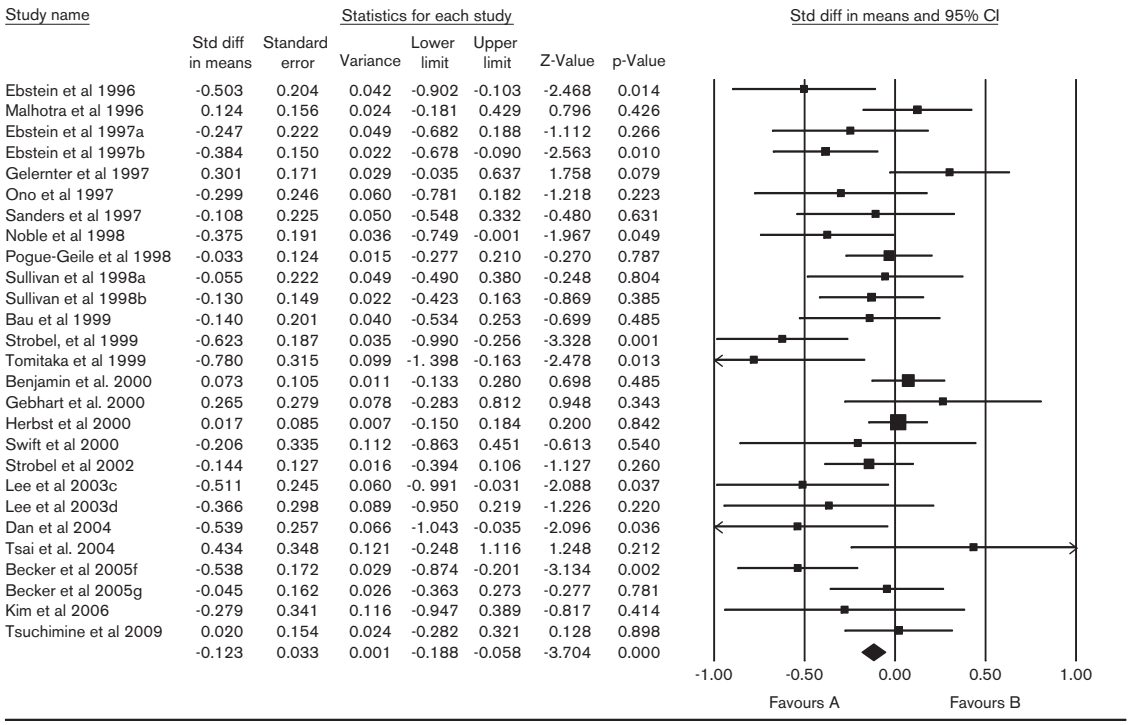
As mentioned above, many studies have reported contradictory or nonsignificant results regarding the association between these two polymorphisms and novelty-seeking. These inconsistent results call for a meta-analysis to provide a more robust estimate. Therefore, the objective of the current study was to reevaluate the associations between the two polymorphisms and novelty-seeking in candidate gene studies. Compared with the previous meta-analyses of *DRD4* (Munafò *et al.*, 2003, 2008), we included newly published studies that have not been used in meta-analysis previously, in addition to including more diverse participants and examining potential moderators to identify sources of heterogeneity and explain the observed inconsistencies. For *DRD4*, we evaluated genotype grouping, sex, mean age, ethnicity, and sample characteristics as modifiers. We also explored the interactions among these moderators. For *COMT*, we included sex, mean age, ethnicity, and sample characteristics as modifiers. These variables have been extensively discussed in previous studies in terms of their effects on the associations between genetic factors and novelty-seeking. To calculate effect sizes, we only selected studies that provided mean, SD, and sample size.

Participants and methods

Literature search

We conducted systematic literature search based on a standardized review protocol (Lipsey and Wilson, 2001). The first step was to identify all molecular genetic

Fig. 1



Overview of meta-analysis of *DRD4* exon III variable number of tandem repeat and novelty-seeking ($k = 27$). CI, confidence interval.

studies on the associations between the two gene polymorphisms (*DRD4* and *COMT*) and novelty-seeking. Therefore, comprehensive searches were performed in two databases (PubMed, PsycINFO) and using the Google Scholar search engine. Search terms were combined to generate results as follows: genetics-related key words (*DRD4* exon III, *COMT*, gene, genetics, genome, epigenetics, single nucleotide polymorphism, genome-wide association study) and trait-related terms (novelty-seeking, impulsivity, sensation-seeking). We also checked references cited in Schinka *et al.* (2002), Kluger *et al.* (2002), and Munafò *et al.* (2003, 2008) for pertinent papers. On the basis of the title, abstract, and full articles, we identified and selected papers that were most closely related to our theme. The eligibility criteria were as follows: (i) the study investigated the association between *DRD4* exon III VNTR and novelty-seeking or between *COMT* Val158Met and novelty-seeking; (ii) the study was an empirical paper published in English and used humans as research participants instead of animal models; and (iii) studies that reported means, SDs, and sample sizes were selected to compute the Cohen's *d* as the effect size. Several studies and samples were excluded because the reported data were not in an appropriate format. Moreover, we only focused on studies that involved measurement of TCI/TPQ. Papers were excluded if they focused on the following: (i) the influence of environmental and context factors on novelty-seeking; (ii) the relationships between novelty-seeking and other personality traits, behaviors, and social outcomes; (iii) the pathology of disorders such as attention-deficit/hyperactivity disorder and hyperactivity-impulsivity; (iv) harm avoidance as one of the sub-scales of personality moderately associated with novelty-seeking, or behavioral disinhibition as a measurement tool and construct to reflect impulsivity (the few molecular studies that involved harm avoidance and disinhibition were excluded to narrow down the traits included); and (v) the linking of candidate genes to brain activities using neurophysiological approaches to address human personality and behavior, rather than direct linking of distal behavior with genetics. Several rounds of supplementary searches were further made to check that we had not missed any important papers.

Data extraction

The literature was coded and data were extracted according to a predetermined standardized coding manual. Moderator variables were also coded. The effect size of Cohen's *d* was calculated using the mean, SD, and sample size of each genotype from each paper. If more than one sample or subgroup was reported, they were calculated as independent entries.

Table 5 Meta-analysis summary statistics for association studies of *DRD4* exon III variable number of tandem repeat with novelty-seeking

		Effect size and 95% confidence interval					Test of null (two tail)		Heterogeneity				τ^2			
Models	Number of studies	Point estimate	SE	Variance	Lower limit	Upper limit	*Z* value	*P* value	*Q* value	*d.f.* (Q)	*P* value	I^2	τ^2	SE	Variance	τ
Fixed	27	−0.123	0.033	0.001	−0.188	−0.058	−3.704	<0.001	53.544	26	0.001	51.442	0.032	0.019	<0.001	0.180
Random effects	27	−0.164	0.051	0.003	−0.265	−0.064	−3.207	0.001								

Data analysis

Data were analyzed using the Comprehensive Meta-Analysis, version 3.0 statistical software (Biostat Inc., Englewood, New Jersey, USA). The *DRD4* exon III VNTR genotypes were classified as '7−' (absence of 7r allele) versus '7+' (presence of 7r allele) or as 's' (four or fewer repeats) versus 'l' (five or more repeats). The *COMT* polymorphisms were grouped as 'Met absence' versus 'Met presence.' Considering that the association was examined as the difference in a continuous variable between dichotomous genotype groups, individual study effect size estimates were calculated with Cohen's *d* to measure standardized differences in mean novelty-seeking scores between carriers and their counterparts, as used in previous studies (Kluger *et al.*, 2002). Data were initially analyzed within a fixed-effect framework. *Q*-statistics were used to test for the homogeneity of effect size estimates, and a χ^2 goodness-of-fit test was used to infer the presence of significant heterogeneity and decide whether to adopt a fixed-effect or random-effect model. Secondary tests were also conducted to explore potential moderators. For *DRD4*, we included genotype grouping (presence/absence of 7r or long/short allele), sex (all-male sample, all-female sample, or mixed sample), mean age (> or <25), ethnicity (Caucasian or Asian), and sample characteristics (normal or abnormal) as modifiers. We also tested age × ethnicity, age × sex, ethnicity × sex, and ethnicity × genotype grouping interactions. An age of 25 years was selected as the threshold for grouping to evenly distribute the samples into two groups. For sex, we also tried to divide the samples into two groups, those with more than 50% female participants and those with less than 50% female participants, to compensate for the limitations of having three groups. For *COMT*, we included sex (percentage of female participants <30%, >0%, or in between), mean age (> or <30), ancestry/ethnicity (primarily Caucasian or Asian), and sample characteristics (normal or abnormal) as modifiers. Funnel plots, classic fail-safe N, and Egger's regression were used to evaluate publication bias.

Results

Description of studies

A description of the studies and samples included in the meta-analysis are presented in Tables 1 and 2, including author information, publication year, measurements, country in which the study was conducted, ethnicity of the participants, sample size, sex percentage, age, source of participants, and moderator variables. For *DRD4*, 24 studies published between 1996 and 2009 were selected according to the inclusion criteria, comprising 27 samples (three studies each reported two different samples). For *COMT*, nine studies published between 2000 and 2011 were selected according to the inclusion criteria, comprising 13 samples (four studies each reported two different samples). Several studies and samples were excluded from the meta-analysis because the available data were not reported in an appropriate format needed to calculate the effect size. For example, Keltikangas-Järvinen *et al.* (2004) and Ray *et al.* (2009) only reported coefficient β, while Staner *et al.* (1998) provided median, minimum, and maximum values, and Lang *et al.* (2007) only offered *F* values. The sample sizes of these three studies are 90, 92, and 37, respectively. Therefore, it was concluded that the exclusion of these small samples could not significantly influence the results. Considering the possibility of overlapping participants in more than one publication, we referred to Munafò *et al.* (2008) and carefully examined the methods sections of each study. Data in Strobel *et al.* (2003) were previously reported in Strobel *et al.* (2002), and hence we used the latter study for our meta-analysis. Lee *et al.* (2003a, 2003b were listed in the study by Munafò *et al.* (2008). Although they were published in the same year and the participants were recruited from junior high schools, there was no sound evidence that they were totally overlapping. As the sample sizes and mean scores were different in these two papers, we retained both in the meta-analysis.

For the *DRD4* analysis, Table 3 shows the allelic frequencies of the samples reported in each study. The results show that 7r is very rare (<5%) in East Asian countries (e.g. Korea, Japan, and China) compared with frequencies in other populations (mostly >15%). In contrast, the frequency of 4r in these East Asian countries was higher (>70%) compared with other countries (mostly <70%).

For the *COMT* analysis, Table 4 shows the allelic and genotype frequencies of the samples reported in each study. The percentage of Met/Met homozygotes was relatively low in East Asian countries compared with the

Table 6 Interactions between moderators of sex, age, genotype grouping and ethnicity in the meta-analysis of association between DRD4 exon III variable number of tandem repeat and novelty-seeking

	Ethnicity				
	Caucasian		Asian		
Moderators	Effect size	*P* value	Effect size	*P* value	Between group *P* value
Sex (three groups)[a]					
All male	−0.322	0.001	–	–	–
Mixed	−0.081	0.050	−0.031	0.826	0.731
All female	−0.186	0.176	−0.348	0.006	0.383
Between group *P* value	0.066	0.093			
Sex (two groups)[a]					
Female percentage < 50%	−0.152	0.004	0.020	0.898 (1 sample)	0.290
Female percentage > 50%	−0.094	0.067	−0.340	0.004	0.057
Between group *P* value	0.431	0.064			
Age (mean)					
< 25	−0.231	< 0.001	−0.265	0.054	0.820
> 25	−0.051	0.267	−0.155	0.227	0.445
Between group *P* value	0.019	0.557			
Genotype grouping					
Short/long grouping	−0.138	0.459	−0.150	0.126	0.953
7r grouping	−0.110	0.002	−0.780	0.013 (1 sample)	0.034
Between group *P* value	0.883	0.056			

'1 sample' means there is only one sample left in this group.
[a]Sex was grouped in two ways.

Table 7 Interactions between moderators of sex and age in the meta-analysis of association between DRD4 exon III variable number of tandem repeat and novelty-seeking

	Age				
	Mean age < 25		Mean age > 25		
Moderators	Effect size	*P* value	Effect size	*P* value	Between group *P* value
Sex (three groups)[a]					
All male	−0.465	< 0.001	−0.126	0.400	0.085
Mixed	−0.186	0.021	−0.042	0.359	0.119
All female	−0.173	0.099	−0.780	0.013 (1 sample)	0.067
Between group *P* value	0.137	0.062			
Sex (two groups)[a]					
Female percentage < 50%	−0.465	< 0.001	−0.076	0.157	0.005
Female percentage > 50%	−0.181	0.005	−0.038	0.600	0.141
Between group *P* value	0.047	0.678			

'1 sample' means there is only one sample left in this group.
[a]Sex was grouped in two ways.

percentages in other samples, which mainly comprised Caucasians.

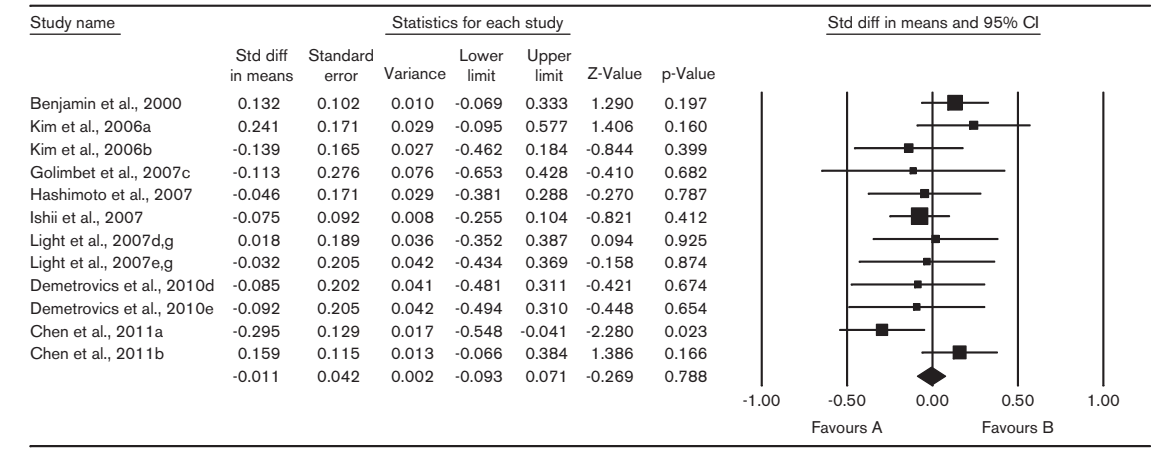
DRD4 polymorphism and novelty-seeking

To analyze the association between the *DRD4* polymorphism and novelty-seeking, the present analysis of 27 independent samples included 4933 participants. As shown in Fig. 1 and Table 5, meta-analysis of the studies resulted in a statistically significant pooled effect size estimate of −0.164, with a 95% confidence interva of −0.265 to −0.064 and included effect sizes ranging from −0.780 to 0.434. This result indicates that the 7r allele is associated with a higher novelty-seeking score. A homogeneity test of the *d*-value produced a significant result ($Q = 53.5$, $d.f. = 26$, $P = 0.001$, $I^2 = 51.4$), indicating between-study variance and the possibility of potential moderators, consistent with previous studies. Hence, a random-effect model is preferred, rather than a fixed-effect model. We also excluded the two studies with the most extreme *d*-values, but the *d*-statistics changed only minimally ($d = -0.160$, $P < 0.001$).

Moderators of the effect of *DRD4* polymorphism on novelty-seeking

Sex and age exerted significant moderating effects between groups. There were significant differences ($P = 0.018$) between all-male samples ($d = -0.322$, $P = 0.001$), mixed samples ($d = -0.077$, $P = 0.052$), and all-female samples ($d = -0.274$, $P = 0.003$). Mean age also served as a moderator ($P = 0.014$). Evidence for association was only found in the younger group ($d = -0.237$, $P < 0.001$) and not in the older group ($d = -0.063$, $P = 0.146$). Other moderators did not show any significant effects, including genotype grouping ($P = 0.758$), ethnicity

Fig. 2



Overview of meta-analysis of *COMT* and novelty-seeking ($k = 12$). CI, confidence interval.

($P = 0.342$), and sample characteristics ($P = 0.878$), but the effect size estimates of the subgroups were all significant.

Although direct moderating effects of ethnicity and genotype grouping were not observed, significant interactions between these and other moderators were detected. First, ethnicity was found to interact with sex (Table 6). In Caucasian samples, the association between the *DRD4* polymorphism and novelty-seeking was stronger in male participants than in female participants ($P = 0.066$); however, in Asian samples, the opposite pattern was observed ($P = 0.064$). There was a significant difference between the associations in Caucasian and Asian females ($P = 0.057$). Second, ethnicity also interacted with age to moderate the contribution of the *DRD4* polymorphism to novelty-seeking (Table 6). The difference between younger and older individuals was much more significant in the Caucasian group ($P = 0.019$) compared with the Asian group ($P = 0.557$). Third, ethnicity and genotype grouping interacted with each other (Table 6). The difference between groupings was significant only among Asian populations ($P = 0.056$), with the 7r allele being more associated with novelty-seeking in Asians than in Caucasians. Fourth, age and sex not only served as independent moderators, but also interacted with each other (Table 7). The association in younger samples differed between sex ($P = 0.047$), indicating that the *DRD4* polymorphism contributed to novelty-seeking more in young males than in young females.

COMT polymorphism and novelty-seeking

The analysis of the association between the *COMT* polymorphism and novelty-seeking included 13 independent samples, comprising 2633 participants. As shown in Fig. 2 and Table 8, meta-analysis of the studies resulted in an insignificant pooled effect size estimate of -0.011 with a 95% confidence interval of -0.093 to 0.071 and effect sizes ranging from -0.295 to 0.241. These results indicated that the *COMT* Val158Met polymorphism was not associated with novelty-seeking. A heterogeneity test of the *d*-values produced a non-significant result ($Q = 12.7$, $d.f. = 11$, $P > 0.05$, $I^2 = 13.555$), indicating that there was no between-study variance. Hence, a fixed-effect model is preferred to a random-effect model. There was no significant change in the results upon removal of the most extreme *d*-value. Of note, the two groups compared in the current study were Met absent (Val/Val) and Met present (Met/Val and Met/Met) carriers. We also calculated the pooled effect size after grouping participants into Val absent (Met/Met) and Val present (Val/Met and Val/Val) carriers, but no significant effect was observed.

Moderators of the effect of *COMT* polymorphism on novelty-seeking

None of the moderating variables tested showed any significant moderating effect, including mean age ($P = 0.594$), ethnicity ($P = 0.769$), and sample characteristics ($P = 0.667$). Moreover, the effect size estimates of the subgroups were not significant. Although evidence of a marginally significant moderating effect was observed for sex percentage ($P = 0.087$), the effect size was not significant.

Publication bias

For the *DRD4* meta-analysis, the *P* value for classic fail-safe N was below 0.001, and the number of missing studies that would bring the *P* value to above 0.05 was 115. The two-tailed *P* value for Egger's regression intercept was significant ($t = 2.13$, $d.f. = 25$, $P = 0.04$),

Table 8 Meta-analysis summary statistics for association studies of *COMT* Val158Met polymorphism with novelty-seeking

		Effect size and 95% confidence interval					Test of null (two tail)		Heterogeneity				Tau-squared			
Models	Number of studies	Point estimate	SE	Variance	Lower limit	Upper limit	*Z* value	*P* value	*Q* value	*d.f.* (*Q*)	*P* value	I^2	τ^2	SE	Variance	τ
Fixed	13	0.015	0.041	0.002	−0.065	0.095	0.370	0.711	21.212	12	0.047	43.427	0.017	0.017	<0.001	0.132
Random effects	13	0.018	0.058	0.003	−0.095	0.131	0.311	0.756								

indicating evidence of publication bias. However, visual inspection of a funnel plot of the SE against the difference in means showed no obvious sign of asymmetry (Fig. 3). For the *COMT* meta-analysis, the *P* value for classic fail-safe N was 0.688, and the two-tailed *P* value for Egger's regression intercept was not significant ($t = 0.12$, $d.f. = 11$, $P = 0.909$). Inspection of a funnel plot (Fig. 4) showed that no obvious publication bias influenced the results of the *COMT* meta-analysis.

Discussion

Meta-analysis of the effects of *DRD4* and *COMT* polymorphisms on novelty-seeking

Our results indicated a statistically significant effect of the *DRD4* exon III VNTR polymorphism on novelty-seeking, and no significant effect of the *COMT* Val158Met polymorphism. A random-effect framework was used in the *DRD4* analysis because of significant heterogeneity, while in the *COMT* analysis, a fixed-effect framework was adopted. Although previous *DRD4* meta-analysis showed no support for an association, our evidence confirmed that the 7r/long allele of the *DRD4* exon III VNTR polymorphism is significantly associated with increased novelty-seeking. One possible explanation for our result is the unified measurement tool that we used. It has been proposed that differences in the measurement tool used to evaluate behavioral tendencies is an important factor generating variance and compromising the significance of small effects, leading to inconsistent results (Light *et al.*, 2007). Therefore, the current study only focused on novelty-seeking scaled by TCI/TPQ to eliminate heterogeneity.

With regard to the *COMT* meta-analysis, the failure to find any significant association could be due to the limited statistical power of the analysis. The pooled effect size estimate of a single genetic variant on a given personality trait may be quite small, thereby requiring a large number of participants to reach statistical significance. Notably, none of the studies included in the *COMT* analysis used more than 500 participants, and the total sample size was only 2633.

Moderators of the effect of *DRD4* and *COMT* polymorphisms on novelty-seeking

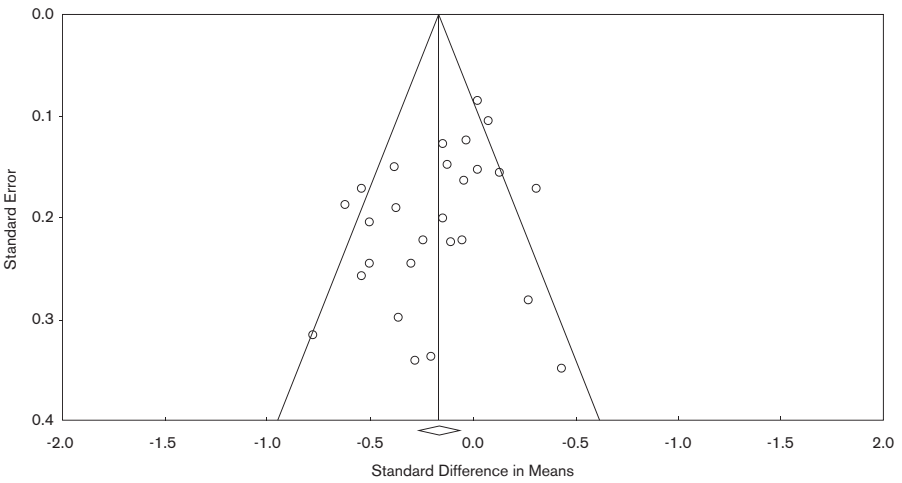
In previous *DRD4* exon III VNTR meta-analyses, age, ethnicity, sex, genotype grouping, and sample characteristics were all examined as moderators, but no evidence of moderating effects was found (Kluger *et al.*, 2002; Munafò *et al.*, 2008). In the current study, except for sample characteristics, which still showed no effect, all other moderators had an effect, with sex and age acting as direct moderators and ethnicity and genotype grouping acting as indirect moderators.

Age has been previously suggested as a moderator (Becker *et al.*, 2005) of the *DRD4* polymorphism. There appears to be a developmental trajectory of novelty-seeking over the life cycle, with an increase in adolescence and a reduction in middle age (Zuckerman *et al.*, 1978). Therefore, our study was consistent with previous studies, suggesting that the association between *DRD4* and novelty-seeking may be best observed in young populations (Kluger *et al.*, 2002).

Although our result was inconsistent with previous meta-analyses (Kluger *et al.*, 2002; Munafò *et al.*, 2008), sex-based differences in the effects of *DRD4* have also been investigated in many association studies. For example, it was previously shown that differences between genotypes were significant in male participants but not in female participants (Becker *et al.*, 2005), indicating that the dopaminergic (genetic) effect plays a more important role in male individuals than in female individuals. Our results were therefore consistent with these findings. However, interestingly, our results also showed that the pooled effect size estimates of the all-male and all-female groups were both higher than that of mixed samples. The explanation for this may lie in the ethnic heterogeneity of the samples. For instance, in studies conducted in Korea (Lee *et al.*, 2003) and Japan (Tomitaka *et al.*, 1999), it was reported that the association between novelty-seeking and the *DRD4* long allele was only found in female participants, not in males.

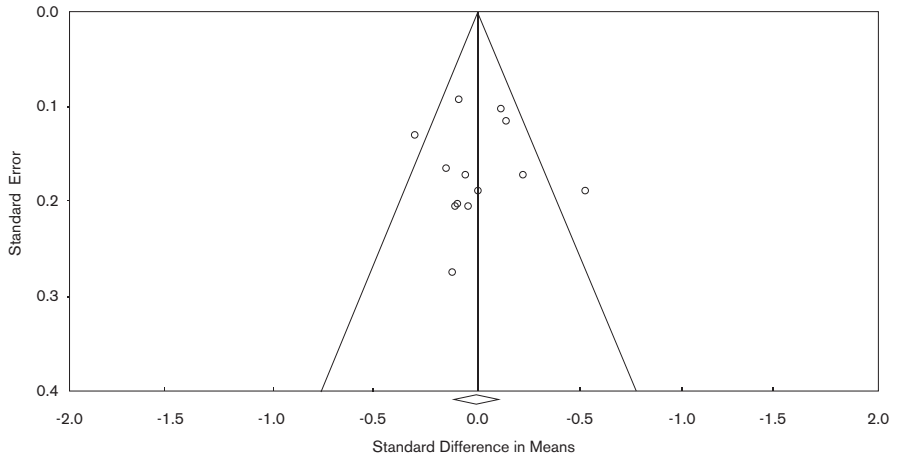
Although ethnicity did not show any direct moderating effect, our results revealed that this variable could interact with other moderators to influence the novelty-seeking personality trait. First, the interaction between sex and ethnicity could explain the inconsistency pertaining to sex differences in the previous studies mentioned above and also the confusing result regarding the mixed samples in our study. The genetic contribution of the *DRD4* polymorphism may be higher in Caucasian males and Asian females. However, it should be noted

Fig. 3



Funnel plot of SE by standard difference in means of the samples included in *DRD4* meta-analysis.

Fig. 4



Funnel plot of SE by standard difference in means of the samples included in *COMT* meta-analysis.

that all-male sample primarily consisted of Caucasian samples, while among Asian studies, there was only one sample for which the percentage of female participants was below 50%. Such biased distributions may somehow reduce statistical power and call for further confirmation. Second, dynamic changes in the association of *DRD4* with novelty-seeking over the course of a life span was found to differ between the Caucasian and Asian groups, indicating an interaction between ethnicity and age, which had not been examined before. Third, although genotype grouping did not show a significant effect alone, as in a previous meta-analysis, it was somehow related to ethnicity. While the 'short/long' grouping has been mostly used in Asian studies (Ebstein and Belmaker, 1997), our study indicated that this grouping strategy may not be appropriate for revealing differences in the genetic contribution of *DRD4* to novelty-seeking; in contrast, the 7r grouping strategy appeared to exhibit better performance, at least in Caucasian samples. This was consistent with the findings of a previous study, which proposed that 'it is unlikely that the short/long genotype grouping would be the defining factor in TCI-measured personality traits' (Tsuchimine *et al.*, 2009). However, it should be noted that all Asian studies adopted the short/long grouping except for one and that the statistical power of this interaction may therefore be reduced.

Our identification of an interaction between sex and age is consistent with previous association studies and

confirmed that sex differences only exist among young individuals (except for one all-female sample). Specifically, clinical and epidemiological studies have reported a significant difference between male and female children and adolescents in various behaviors, for example, preschool boys score higher on novelty-seeking (Constantino *et al.*, 2002) and male adolescents score higher on sensation-seeking (Martin *et al.*, 2002). Our results not only imply that male 7r carriers exhibit increased novelty-seeking behavior compared with females at an early age but also indicate that these behaviors are likely to decline with age, resulting in similar novelty-seeking between males and females in older individuals.

With regard to the sample characteristics, although evidence of an association between the *DRD4* polymorphism and novelty-seeking was confirmed in the abnormal group, our results were concordant with a previous meta-analysis (Munafò *et al.*, 2008) in that there was no support for a difference between unselected and selected samples. However, we still cannot rule out the possibility that the *DRD4* polymorphism may be associated with novelty-seeking to a different extent in the presence of various traits. One reason for this uncertainty is the heterogeneity in the selected characteristics. For example, a stronger association with novelty-seeking was observed in 7r carriers with fibromyalgia (Dan *et al.*, 2004), and a lower association was observed in African American substance abusers (Gelernter *et al.*, 1997), while no association has been observed in alcoholics (Sander *et al.*, 1997) and participants with depression (Sullivan *et al.*, 1998). These inconsistent results may mask real associations within each symptom or trait.

For the nonsignificant association between novelty-seeking and the *COMT* polymorphism, no moderating effect was observed with any of the moderators analyzed. Although it has been reported that sex may modulate associations between the *COMT* Val158Met polymorphism and personality traits (Chen *et al.*, 2011), we failed to identify any sex difference in this study. The same result was observed for sample characteristics (e.g. opiate-dependent patients) and was consistent with previous studies, demonstrating that the effect of *COMT* on novelty-seeking is not drug-specific (Demetrovics *et al.*, 2010).

Conclusion

The evidence from our meta-analysis indicates that there is a statistically significant effect of the *DRD4* exon III VNTR polymorphism on novelty-seeking, but no association between *COMT* the Val158Met polymorphism and novelty-seeking. Age and sex are direct moderators of the *DRD4* effect, while ethnicity and genotype grouping are indirect moderators. Ethnicity interacts with age, sex, and genotype grouping, and age and sex interact with each other, to moderate the association between the *DRD4* exon III VNTR polymorphism and novelty-seeking.

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Conflicts of interest

There are no conflicts of interest.

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