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ORIGINAL RESEARCH

Genetic Variation at the *TPH2* Gene Influences Impulsivity in Addition to Eating Disorders

Margarita C. T. Slof-Op't Landt · Meike Bartels · Christel M. Middeldorp · Catherina E. M. van Beijsterveldt · P. Eline Slagboom · Dorret I. Boomsma · Eric F. van Furth · Ingrid Meulenbelt

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Abstract Genes are involved in eating disorders (EDs) and self-induced vomiting (SV), a key symptom of different types of EDs. Perfectionism and impulsivity are potential risk factors for EDs. *TPH2* (tryptophan hydroxylase 2) SNP rs1473473 was previously associated with anorexia nervosa and EDs characterized by SV. Could perfectionism or impulsivity be underlying the association between rs1473473 and EDs? Genetic association between *TPH2* SNP rs1473473 and perfectionism or impulsivity was first evaluated in a random control group ($N = 512$). The associations obtained in this control group were subsequently tested in a group of patients with an ED ($N = 267$). The minor allele of rs1473473 (OR = 1.49) was more frequent in impulsive controls, but also in impulsive patients with an ED (OR = 1.83). The largest effect was found in the patients with an ED characterized by SV (OR = 2.51, $p = 0.02$). Genetic variation at the *TPH2* gene appeared to affect impulsivity which, in turn, might predispose to the SV phenotype.

Keywords Eating disorders · Perfectionism · Impulsivity · *TPH2* · Association analysis

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M. C. T. Slof-Op't Landt (✉) · E. F. van Furth
Center for Eating Disorders Ursula, P. O. Box 422, 2260 AK Leidschendam, The Netherlands
e-mail: r.optlandt@centrumeetstoornissen.nl

M. C. T. Slof-Op't Landt · P. E. Slagboom · I. Meulenbelt
Department of Medical Statistics, Molecular Epidemiology Section, Leiden University Medical Centre, Leiden, The Netherlands

M. C. T. Slof-Op't Landt · M. Bartels · C. M. Middeldorp · C. E. M. van Beijsterveldt · D. I. Boomsma
Department of Biological Psychology, VU University, Amsterdam, The Netherlands

C. M. Middeldorp
Department of Child and Adolescent Psychiatry, Academic Medical Center Amsterdam, Amsterdam, The Netherlands

C. M. Middeldorp
Department of Child and Adolescent Psychiatry, GGZ inGeest, VU Medical Center, Amsterdam, The Netherlands

P. E. Slagboom
Netherlands Consortium for Healthy Ageing, Leiden University Medical Center, Leiden, The Netherlands

Introduction

The most familiar and well-described eating disorders (EDs) are anorexia nervosa (AN) and bulimia nervosa (BN). However, the majority of ED patients (about 60 %) do not meet strict Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV(American Psychiatric Association 1994)) diagnostic criteria for either of these types, and therefore belong to the 'ED not otherwise specified' category (Fairburn and Bohn 2005). An important symptom that is common in different types of ED (in about 35 % of AN patients, and 90 % of BN patients) is self-induced vomiting (SV), a method to lose body weight or prevent weight gain (Ben-Tovim et al. 1989; Garner et al. 1993).

In our study (Slof-Op 't Landt et al. 2011), we observed a significant association between the minor C-allele of the *TPH2* single nucleotide polymorphism (SNP) rs1473473 and AN as well as EDs characterized by SV. This association was subsequently replicated in a meta-analysis with

two additional independent case-control samples (AN: odds ratio [OR] = 1.25, 95 % confidence interval [CI] 1.06–1.47, $p < 0.01$; SV: OR = 1.34, 95 % CI 1.06–1.69, $p < 0.01$) (Slof-Op 't Landt et al. 2011). The *TPH2* gene encodes the enzyme tryptophan hydroxylase in the brain (Zill et al. 2007), which is involved in the first and rate-determining step in the biosynthesis of the neurotransmitter serotonin. We hypothesized that the association acts through variation in serotonin activity.

Impulsivity, a moderately heritable personality feature, is consistently associated with decreased serotonin activity in both non-clinical populations and ED groups (Bruce et al. 2005; Carver and Miller 2006; Hur and Bouchard 1997; Pedersen et al. 1988; Racine et al. 2009; Seroczynski et al. 1999; Steiger et al. 2001; Steiger et al. 2005). A recent review pointed out that impulsivity can differentiate individuals with an ED from controls (Waxman 2009). Also after recovery from an ED impulsivity remains higher in certain groups of recovered women compared to control women (Wagner et al. 2006). In general, the ED groups characterized by binge eating (AN binge-purging type, BN) show more impulsivity than participants with restricting type AN (Waxman 2009). This link may be explained by the presence of binge eating alone. Fernandez-Aranda et al. (2008) found that impulse control disorders were associated with binge eating within a group of patients with different types of EDs. However, other studies have found that the presence of impulsivity in the 'binge' EDs is not solely explained by the symptom of binge eating, but that purging behaviors appear to be involved as well. Both binge eating and purging were associated with substance abuse/dependence in women with AN (Root et al. 2010). In addition, no difference in impulsivity scores were found between patients with purging disorders (characterized by purging in the absence of objective binge eating episodes) and patients with BN (Brown et al. 2011; Keel et al. 2005). Two studies even reported that the presence of purging behavior and not binge eating was associated with impulsivity scores and the presence of impulsive behaviors in AN and/or BN (Favaro et al. 2005; Hoffman et al. 2012). Possibly the type of purging behavior (for example SV, use of laxatives or diuretics) that patients use is also important. Although not controlled for the occurrence of binge eating, higher scores on the novelty-seeking scale of the temperament and character inventory (Cloninger et al. 1993) were found in patients with an ED who engage in SV compared with patients who do not engage in this behavior (Dalle Grave et al. 2009; Reba et al. 2005). Components of impulsivity are assessed by this novelty-seeking scale.

Another heritable personality characteristic which is associated with different types of EDs is perfectionism (Cassin and von Ranson 2005; Steiger et al. 2004; Tozzi et al. 2004). High levels of perfectionism seem to be present before the onset of EDs (Fairburn et al. 1997; Fairburn et al. 1999; Lilenfeld et al. 2006), and also remain present after recovery (Achenbach 1991; Bastiani et al. 1995; Lilenfeld et al. 2000; Srinivasagam et al. 1995). Kaye et al. (1991) was the first to hypothesize that increased serotonin activity might be associated to core behaviors of AN, like perfectionism. Steiger et al. (2004) tested whether compulsive personality traits, including perfectionism might correspond to elevated serotonin activity in women with bulimia-spectrum ED. Cluster analyses based on serotonin functioning among the patients with BN revealed that two clusters could be defined, one was characterized by low density of receptor binding sites and high binding affinity while another was characterized by high binding with low affinity. The patients in the second cluster (high density of binding sites) showed elevated levels of perfectionism compared with normal-eater controls. This result suggests that perfectionism might be linked to elevated serotonin activity.

These observations raise the question whether *TPH2* affects EDs (characterized by SV) via the personality traits impulsivity and/or perfectionism (Slof-Op 't Landt et al. 2011). In the current study, we therefore investigated whether impulsivity and/or perfectionism was underlying the association between *TPH2* SNP rs147373 and EDs (AN or EDs characterized by SV). Because perfectionism and impulsivity are associated with EDs, the disease state is expected to influence the scores on the self-report measures of perfectionism and impulsivity. Therefore the association between *TPH2* rs1473473 and perfectionism and/or impulsivity was first investigated in a population-based control group of women ($N = 512$) from the Netherlands twin registry (NTR). The observed associations within this control group, were subsequently tested in a group of patients with an ED ($N = 267$) from the GenED study (Slof-Op 't Landt et al. 2011). The analyses were performed in the total ED group, in patients with restricting-type AN ($N = 87$), and in patients with an ED characterized by SV ($N = 149$).

Methods

Participants

This study was approved by the ethics committee of the VU university and by the ethics committee for mental health institutions in the Netherlands (METiGG). All participants gave written informed consent.

The NTR was established in the late 1980s at the VU University in Amsterdam, the Netherlands. Data on the multiples (twins or triplets) and their family members have been collected every 2–3 years in longitudinal survey

studies (Bartels et al. 2007; Boomsma et al. 2002; Boomsma et al. 2006). Subsamples were invited to participate in experimental and laboratory studies and provide DNA samples (Boomsma et al. 2006). In the current study, data for a total of 512 random unrelated women from the NTR were analyzed. Lifetime prevalence in women ranges between 0.9–3.5 for different types of EDs (Hudson et al. 2007; Preti et al. 2009). Because of this low prevalence only a small number of women will be affected in the population. Therefore the control women were not screened for the absence or presence of an ED.

At ten specialist ED units throughout the Netherlands, consecutive patients who were seeking treatment for their ED were asked to participate in the GenED study. DSM-IV ED diagnoses were made by experienced clinicians based on a semi-structured interview (Fairburn and Cooper 1993; Keller et al. 1987; Krämer 1996) at intake, and by the self-report eating disorder examination questionnaire (EDEQ) (Fairburn and Beglin 1994) if diagnosis at intake was not available. Similar to our previous study (Slof-Op 't Landt et al. 2011), a selection of female patients with AN or an ED characterized by SV was included in the current study. This group ($N = 267$) consisted of 182 patients with AN (87 restricting type, 32 binge-purging type, and 55 purging without binge eating and 8 binge eating without purging, respectively), 74 patients with BN and 11 patients with an ED not otherwise specified. Regular SV (>2 times/month) was reported by 149 patients (64 AN purging type, 74 BN and 11 ED not otherwise specified; 102 of these patients reported objective binge eating, 134 reported either objective or subjective binge eating).

Measures

Phenotype

The young adult self report (YASR) (Achenbach 1990) and the youth self report (YSR) (Levinson 2005; Verhulst et al. 1997) questionnaires belong to the Achenbach system of empirically based assessment (ASEBA, www.aseba.org), which provides age-adjusted instruments to assess similar facets of maladaptive functioning from 1.5 to 90 year. Responses were given on a three-point scale, with the code 0 if the item was not true, 1 for sometimes true, and 2 for often true. Substantial test–retest reliabilities have been found for the different subscales of the YSR and YASR, with r ranging between 0.67 and 0.94 (www.aseba.org). For the current study, two items (item 32, 'I feel that I have to be perfect'; and item 41, 'I act without stopping to think') from the YSR/YASR questionnaire were used to measure perfectionism and impulsivity. The YASR/YSR items were available for the complete control group and for a subgroup of the patients with an ED ($N = 79$).

The multidimensional perfectionism scale (MPS) by Frost et al. (1990) is a 36-item questionnaire which distinguishes six dimensions of perfectionism (concern over mistakes, personal standards, parental expectations, parental criticism, doubt about actions, and organization), and yields a global perfectionism score. Responses were given on five-point Likert scales, ranging from 'strongly disagree' to 'strongly agree'. MPS data were available for the complete ED group from the GenED study.

The Dickman impulsivity inventory (DII) (Dickman 1990) is a 23-item questionnaire with responses in a true/false answer format. This instrument distinguishes two forms of impulsivity: dysfunctional impulsivity (the tendency to engage in rapid, error-prone information processing in situations where this is non-optimal) and functional impulsivity (the tendency to engage in rapid, error-prone information processing when such a strategy is rendered optimal). In the current study, data for the dysfunctional impulsivity scale were used. Whiteside and Lynam (2001) showed that this dysfunctional impulsivity scale loads on the same underlying factor as the impulsivity subscale of the temperament and character inventory (Cloninger et al. 1993), suggesting that these scales measure the same underlying construct. DII data were available for the complete ED group from the GenED study.

Genotype

Genomic DNA was isolated from buccal swabs (ED group, 40 % of control group) and blood samples (60 % of control group). Previously, ten *TPH2* tagging SNPs were selected from HapMap and genotyped by mass spectrometry (homogeneous MassARRAY system; Sequenom, San Diego, CA, USA) using standard conditions (Middeldorp et al. 2010; Slof-Op 't Landt et al. 2011). PCR reactions were carried out in a final volume of 5 µl and contained standard reagents and 2.5 ng of genomic DNA. In the current study, only the genotypes for *TPH2* rs1473473, which was associated with AN and EDs characterized by SV in our previous study (Slof-Op 't Landt et al. 2011), were analyzed.

Statistical analyses

Pearson's χ^2 statistics were calculated to compare response frequencies of perfectionism and impulsivity (YSR/YASR) between control women and the subgroup of patients with an ED. Within the ED group, response frequencies of the YSR/YASR items (Pearson's χ^2 statistics) and means for the global perfectionism score (MPS) (analysis of variance) were compared between patients with restricting-type AN and patients with an ED characterized by SV. The nonparametric Mann–Whitney U test was performed to

compare the dysfunctional impulsivity scale between patients with restricting-type AN and patients with an ED characterized by SV.

The minor allele frequency (MAF) of *TPH2* rs1473473 was compared between the different YSR/YASR perfectionism and impulsivity categories in the control group by Pearson's χ^2 statistics. Nominal significant associations ($p < 0.05$) between rs1473473 and perfectionism or impulsivity, were subsequently tested in the complete ED sample, the patients with restricting-type AN, and the patients with an ED characterized by SV.

In case of a significant association between rs1473473 and a personality feature (perfectionism and/or impulsivity) in both the control group and the ED sample, the three-step mediation approach as described by Baron and Kenny (1986) was performed. Logistic regression analyses were used. First, the personality feature (mediator) is regressed on rs1473473 (independent variable). In the second step the outcome variable EDs (characterized by SV) is regressed on rs1473473. In the third and final step, the outcome variable EDs (characterized by SV) is regressed on both rs1473473 as well as the personality feature. All statistical analyses were performed in SPSS version 16 (SPSS, Chicago, IL, USA).

Results

The control women were, on average, 28.7 (range 13–61.6, SD = 14.8) years old and had a mean body mass index (BMI) of 22.9 (SD = 4.1) kg/m^2. The total ED group was on average 28.6 (range 16.1–61.3, SD = 9.8) years old and had a mean BMI of 18.75 (SD = 4.9) kg/m^2. The ED subgroup, consisting of 79 patients for whom data on the YSR/YASR items as well as the MPS and DII were present, was on average 30.1 (range 16.8–61.3, SD = 10.6) years old and had a mean BMI of 18.1 (SD = 4.6) kg/m^2.

Perfectionism

In supplementary Table 1, the response frequencies for the YSR/YASR perfectionism item and the mean of the global perfectionism score of the MPS are presented. Within the ED subgroup, a biserial correlation of 0.4 was observed between the categorical YSR/YASR perfectionism item and the global perfectionism score. In the ED subgroup, the majority of the patients (79.7 %) reported that they often had the feeling they had to be perfect, while only 10.9 % of the control women reported this (χ^2 (2) = 203.8, $p < 0.001$). Within the subgroup, all the patients with restricting type AN reported that they often had the feeling that they had to be perfect compared with 72.2 % of the group characterized by SV (χ^2 (2) = 5.9, $p = 0.05$). No significant differences were observed in the MPS global perfectionism score between the SV and restricting AN group, either in the ED subgroup or in the total ED group (F (1,65) = 2.1, F (1,221) = 0.2 respectively).

Within the control group, no differences were observed in the MAF of *TPH2* rs1473473 for the three YSR/YASR perfectionism categories, observed MAF were 0.13, 0.16, and 0.12, respectively.

Impulsivity

In Table 1, the response frequencies for the YSR/YASR impulsivity item and the mean of the dysfunctional impulsivity scale of the DII are presented. Within the ED subgroup, a biserial correlation of 0.7 was observed between the categorical YSR/YASR impulsivity item and the dysfunctional impulsivity scale. In the ED subgroup, 15.2 % of the patients reported that they often act impulsively compared with 4.5 % of the control group (χ^2 (2) = 15.4, $p < 0.001$). Within the ED subgroup, none of the patients with restricting type AN reported that they often act impulsively compared with 16.7 % of the SV group (χ^2 (2) = 9.6, $p = 0.01$). This difference was also observed in the dysfunctional impulsivity scale of the DII, within the ED subgroup the mean scores were 1.6 (median 1.0) for restricting type AN and 3.7 (median 3.0) for patients with an ED characterized by SV (Mann–Whitney $U = 279.5$, $p = 0.02$). In the total ED group, the scores for dysfunctional impulsivity were 1.8 (median 1.0) for restricting type AN and 3.4 (median 2.0) for SV (Mann–Whitney $U = 4349.5$, $p < 0.001$).

Because less than 5 % of the control group reported an impulsivity score of 2 (Table 1), the responses were merged into two impulsivity categories (absent/present) for the genetic analysis. In the top section of Table 2, the MAF of *TPH2* rs1473473 is shown per category for the YSR/YASR impulsivity item in the control group. The MAF of rs1473473 was higher in the impulsive controls compared with the non-impulsive controls (χ^2 (1) = 4.3, OR = 1.49, 95 % CI 1.02–2.17, $p = 0.04$). The association between rs1473473 and impulsivity was subsequently tested in the ED group.

At the bottom of Table 2, the results from the genetic analyses in the ED subgroup and the total ED group are presented. In accordance with the control group, two impulsivity categories were used (absent/present) based on the YSR/YASR item in the ED subgroup. To create an impulsivity measure that was equivalent to YSR/YASR impulsivity item, the dysfunctional impulsivity scale was also merged into two categories. Based on the frequencies of the YSR/YASR item in the ED subgroup (see Table 1: 34.2 % absent vs. 65.8 % present) a cut-off value of 1 was chosen for the dysfunctional impulsivity scale to create

Table 1 Response frequencies on the YSR/YASR impulsivity item and mean and median scores on the dysfunctional impulsivity scale for the control women (YSR/YASR), a subgroup of patients with an ED (YSR/YASR and dysfunctional impulsivity) and the total ED group (dysfunctional impulsivity)

Group	Subsample	N	Scale	Mean (median)	Response frequencies (%)		
					0	1	2
Control	NTR women	512	YSR/YASR impulsivity	–	45.9	49.6	4.5
ED subgroup	Complete	79	YSR/YASR impulsivity	–	34.2	50.6	15.2
			Dysfunctional impulsivity (DII)	3.3 (3.0)	–	–	–
	Anr	17	YSR/YASR impulsivity	–	64.7	35.3	0
			Dysfunctional impulsivity (DII)	1.6 (1.0)	–	–	–
	SV	54	YSR/YASR impulsivity	–	25.9	57.4	16.7
			Dysfunctional impulsivity (DII)	3.7 (3.0)	–	–	–
ED total group	Complete	267	Dysfunctional impulsivity (DII)	2.9 (2.0)	–	–	–
	Anr	87	Dysfunctional impulsivity (DII)	1.8 (1.0)	–	–	–
	SV	149	Dysfunctional impulsivity (DII)	3.4 (2.0)	–	–	–

NTR Netherlands twin registry, *ED* eating disorder, *ANr* anorexia nervosa restricting type, *SV* self-induced vomiting, *YSR* youth self report, *YASR* young adult self report, *DII* Dickman impulsivity inventory

Table 2 Allelic association of *TPH2* SNP rs1437473 with impulsivity in the control group and patients with an ED

Group	Scale	*N*	Alleles	Impulsivity absent		Impulsivity present		OR (95 % CI)	*p*
				N	MAF	*N*	MAF		
Control	YSR/YASR impulsivity	478	T > C	218	0.12	260	0.16	**1.49 (1.02, 2.17)**	**0.04**
ED subgroup	YSR/YASR impulsivity	79	T > C	27	0.15	52	0.25	1.92 (0.80, 4.59)	0.14
ED total group	Dysfunctional impulsivity (DII)	258	T > C	80	0.13	178	0.22	**1.83 (1.08, 3.08)**	**0.02**
Anr	Dysfunctional impulsivity (DII)	87	T > C	38	0.13	49	0.20	1.69 (0.74, 3.87)	0.21
SV	Dysfunctional impulsivity (DII)	141	T > C	38	0.11	103	0.23	**2.51 (1.13, 5.60)**	**0.02**

ED eating disorder, *ANr* anorexia nervosa restricting type, *SV* self-induced vomiting, *YSR* youth self report, *YASR* young adult self report, *DII* Dickman impulsivity inventory, *MAF* minor allele frequency, *OR* odds ratio, *CI* confidence interval

Bold values indicate a nominal significant association with a *p*-value below 0.05

similar rates in the complete ED group, 31 % were non-impulsive (score = 0), 69 % were impulsive (scores > 0).

Within the ED subgroup, the MAF of rs1473473 was higher in the impulsive compared with the non-impulsive patients, albeit not significantly (14.8 vs. 25.0 %, χ^2 (1) = 2.2, $p = 0.14$). In the total ED group, the MAF of rs1473473 was higher in the impulsive compared with the non-impulsive patients (χ^2 (1) = 5.2, OR = 1.83, 95 % CI 1.08–3.08, $p = 0.02$). This association could not be found in the patients with restricting type AN (χ^2 (1) = 1.6, $p = 0.21$), but was present in the patients with an ED characterized by SV (χ^2 (1) = 5.3, OR = 2.51, 95 % CI 1.13–5.60, $p = 0.02$).

Mediation

As described by Baron and Kenny (1986), mediation would be suggested if (1) rs1473473 is significantly associated to impulsivity, (2) rs1473473 is significantly associated to ED (characterized by SV), and (3) the association between rs1473473 and ED (characterized by SV) decreases (or goes to zero) when impulsivity is entered into the equation.

Table 3 Mediation analyses following the three-steps mediation approach of Baron & Kenny to test if YSR/YASR impulsivity is a mediator for the association between rs1473473 and EDs or EDs characterized by SV

	Dependent variable	Independepent variable	*B*	S.E.	Wald	df	*p*	OR (95 % CI)
Eating disorders								
Step 1	YSR/YASR impulsivity	Rs1473473 (allele)	0.45	0.18	6.65	1	0.01	1.57 (1.11, 2.21)
Step 2	ED	Rs1473473 (allele)	0.38	0.14	7.30	1	0.007	1.46 (1.11, 1.92)
Step 2[a]	ED	Rs1473473 (allele)	0.52	0.22	5.86	1	0.02	1.68 (1.10, 2.56)
Step 3	ED	Rs1473473 (allele)	0.48	0.22	4.82	1	0.03	1.61 (1.05, 2.46)
		YSR/YASR impulsivity	0.45	0.18	6.21	1	0.01	1.57 (1.10, 2.24)
Eating disorders characterized by self-induced vomiting								
Step 1	YSR/YASR impulsivity	Rs1473473 (allele)	0.45	0.18	6.65	1	0.01	1.57 (1.11, 2.21)
Step 2	SV	Rs1473473 (allele)	0.38	0.17	4.99	1	0.03	1.47 (1.05, 2.05)
Step 2[a]	SV	Rs1473473 (allele)	0.45	0.26	3.09	1	0.08	1.57 (0.95, 2.59)
Step 3	SV	Rs1473473 (allele)	0.38	0.26	2.16	1	0.14	1.46 (0.88, 2.43)
		YSR/YASR impulsivity	0.85	0.23	13.85	1	0.0002	2.35 (1.49, 3.68)

YSR youth self report, *YASR* young adult self report, *ED* eating disorder, *SV* self-induced vomiting, *OR* odds ratio, *CI* confidence interval

[a] Logistic regression in the sample with YSR/YASR impulsivity data

In Table 3 these three steps are presented for the outcome variable EDs as well as the outcome variable EDs characterized by SV. Because only a subgroup of the patients ($n = 79$) had YSR/YASR impulsivity data, the results of step 2 (the association between rs1473473 and EDs) are shown for both the total ED group as well as the subgroup.

In the mediation analyses with outcome variable EDs impulsivity could not be identified as a mediator. When entering impulsivity into the equation, the association between rs1473473 and EDs decreased slightly but remained significant. In the analyses with EDs characterized by SV, the effect of rs1473473 on EDs characterized by SV decreased from trend-significant to non-significant after entering impulsivity into the logistic regression analysis. Impulsivity therefore might be a mediator for the association between *TPH2* rs1473473 and EDs characterized by SV.

Discussion

In the current study, we investigated whether the previous association between *TPH2*, AN and EDs characterized by SV (Slof-Op 't Landt et al. 2011) was explained by differences in the underlying personality traits perfectionism and impulsivity. In a population-based control group, the *TPH2* SNP rs1473473 was significantly associated with higher impulsivity (OR = 1.49), which was subsequently confirmed in an analyses in patients with an ED (OR = 1.83). The association in the ED group appeared to be caused especially by the patients with an ED characterized by SV. In this group, carriers of the minor allele of rs1473473 had the highest risk of reporting impulsivity (OR = 2.51). In a final mediation analyses in the ED subgroup and control women, the effect of rs1473473 on SV appeared to be mediated by impulsivity. Given these results, we hypothesize that *TPH2* rs1473473 is associated with a lower activity of the *TPH2* gene. As a consequence, less serotonin will be synthesized in the brain, leading to a lower serotonin neurotransmission. Lower serotonin activity is associated with higher impulsivity. High impulsivity may make people more prone to engage in binge eating and SV, and in this way predispose them to the development of an ED (characterized by SV).

Our findings are in line with previous observations, in both animals and humans, that increased serotonin neurotransmission leads to reduced eating behavior, whereas decreased neurotransmission precedes compulsive or binge eating (Blundell 1986; Simansky 1996; Steiger 2004). Furthermore, in EDs, the serotonin system has been found to be dysregulated; lower levels of serotonin metabolites were observed in patients with AN, and less functional activity of the central serotonin system was observed in patients with AN or BN (Brewerton and Jimerson 1996; Kaye et al. 2005; Monteleone et al. 2000). Moreover, after recovery, higher levels of serotonin metabolites have been found for AN (Kaye et al. 1991). Studies in patients that recovered from BN showed mixed results with indications for reduced, normalized, and increased serotonin activity (Kaye et al. 1998; Kaye et al. 2001; Wolfe et al. 2000). Impulsivity has been linked to reduced serotonin activity in non-clinical populations, in clinical psychiatric samples and in patients with BN (Bruce et al. 2005; Carver and Miller 2006; Racine et al. 2009; Steiger et al. 2001; Steiger et al. 2005). Finally, genetic variation at the *TPH2* gene has been associated with cognitive impulsivity (Oades et al. 2008), suicide attempts (Yoon and Kim 2009; Zhou et al. 2005; Zill et al. 2004), and response inhibition (Stoltenberg et al. 2006), behaviors that are linked to impulsivity

(Congdon and Canli 2008). Rs1473473 is not in LD with known *TPH2* mutations (Haavik et al. 2008). *TPH2* SNPs in LD with rs1473473 however, have been associated with a suicidal mental condition in Finnish men (Zhou et al. 2005), with antidepressant response in depressive patients (Peters et al. 2004), and with allelic mRNA expression imbalance in sections of the human pons (Lim et al. 2007).

Despite a previous study that showed an association between perfectionism and 'high serotonin reuptake density' in a subgroup of patients with BN (Steiger et al. 2004), we could not detect any effect between *TPH2* and perfectionism. The correlation between YSR/YASR perfectionism and the MPS global score was moderate ($r = 0.41$), suggesting that these scales might not measure the same underlying trait. So it is possible that other measures of perfectionism (like the MPS) might still be associated to *TPH2*. It could also be that other serotonin genes (Barnes and Sharp 1999) underlie the 'high serotonin reuptake density' instead of *TPH2*. Furthermore, the association between perfectionism and the serotonin system could be present only in a subgroup of patients with BN, and thus might not be found in a population-based sample of women.

To allow genetic association to a consistent impulsivity and perfectionism trait across our study populations, we could only use a single item in the control group to assess impulsivity and perfectionism. This is a drawback because as a result, we were not able to capture the complete multidimensional construct of both characteristics. To allow association to all dimensions of the traits and to replicate our findings, additional analyses are necessary. However, since the correlation between the YSR/YASR impulsivity item and the dysfunctional impulsivity scale was considerable (0.70), they are probably measuring the same underlying construct. The dysfunctional impulsivity scale was found to be part of the impulsivity dimension 'Lack of Planning' (Whiteside and Lynam 2001). This dimension has been associated with BN symptoms in a study by Fischer et al. (2008). Because the dysfunctional impulsivity scale had a positively skewed distribution, with 31 % of the patients with an ED scoring 0, the scale could not be used as a continuous measure in a parametric statistical test. In accordance with the distribution of the impulsivity item used in the control group, the dysfunctional impulsivity scale was divided into two categories. In future studies, we hope to elucidate the association between impulsivity (as a continuous or ordinal multidimensional characteristic) and the *TPH2* gene further in a larger sample of patients with an ED.

Whether binge eating, purging or both are associated with the differences found in impulsivity between subtypes of EDs (Waxman 2009) is under debate. Since 90 % of our SV sample reports binge eating, it is possible that the symptom of binge eating underlies the reported association between SV and *TPH2* rs1473473. In the current study, only patients with AN or an ED characterized by SV were selected. Within this study design it was not possible to properly examine SV versus binge eating. It is important to disentangle the effect of these two behaviors in future studies.

Finally, in the present study design, we could only test whether the association between impulsivity and *TPH2* was underlying the previously reported association between ED and *TPH2* (Slof-Op 't Landt et al. 2011) in a small subset of the patients with an ED. Due to the smaller sample size of the subset, the association between rs1473473 and SV only reached trend-significance. Therefore the results from this mediation analyses should be seen as preliminary, and replication in a larger study is required. Because impulsivity was measured in the acute phase of the ED, it remains possible that impulsivity is a consequence of rather than a predisposing feature for the ED. However other studies have reported that impulse control disorders and engaging in impulsive behaviors precedes the onset of EDs in a majority of the patients (62–80 %) (Fernandez-Aranda et al. 2008; Nagata et al. 2000).

The etiology of EDs is still largely unknown. Presumably genetic factors, personality features, and environmental influences interact in the development of these disorders (Jacobi et al. 2004; Stice 2002). Although there seems to be a shared liability between the different types of EDs (Bulik et al. 2010; Strober et al. 2000), our results also indicate the importance of unique influences on different types of EDs. The *TPH2* gene affects impulsivity which in turn might predispose to the SV phenotype. Further studies are necessary to determine the direction of causation.

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