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ORIGINAL ARTICLE

Symmetry symptoms in obsessive-compulsive disorder: clinical and genetic correlates

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Objective: In obsessive-compulsive disorder (OCD), symmetry-related symptoms may be important. Although clinical correlates of symmetry-related symptoms have been identified in OCD, few data exist on genetic associations. Animal studies indicate involvement of dopamine in symmetry-related behavior, suggesting this may be relevant to analogous symptoms in OCD. Alterations in dopamine may also reflect environmental influences. However, the association of symmetry-related symptomatology, early adversity, and polymorphisms in dopaminergic genes has not been investigated in OCD.
Methods: Clinical information and polymorphisms in key dopaminergic genes were compared between OCD patients with primary symmetry symptoms and those without.
Results: OCD patients with primary symmetry symptoms comprised 46.6% (n=210) of the sample (n=451), and were older ($p < 0.01$), had longer illness duration ($p < 0.01$), higher OCD severity scores ($p = 0.01$), and greater comorbidity ($p < 0.01$) than those without. In Caucasians (n=343), genotype frequency differed significantly between groups for *ANKK1* rs1800497, with more OCD patients with symmetry symptoms being homozygous for the *A2* (*CC*) genotype ($\chi^2 = 7.296$; $p = 0.026$).
Conclusion: Symmetry symptoms have some distinct clinical features and may represent a marker of severity in OCD. However, clinical associations, in combination with the association found with the *ANKK1* rs1800497 *A2* variant, suggest that primary symmetry symptoms may represent a distinctive clinical and psychobiological profile.

Keywords: Obsessive-compulsive disorder; symptom subtype; trauma; genetics; dopamine

Introduction

There are many definitions of symmetry, which vary depending on context. Typically, however, symmetry refers to a characteristic feature of an object where one half appears to mirror the other half. Symmetry may also relate to living organisms, including humans and animals. The body of most multicellular organisms exhibits some form of symmetry. In humans, for example, facial symmetry generally is one of a number of traits associated with health and beauty. Indeed, some literature suggests that symmetry is an important indicator of "freedom from disease, and worthiness for mating"[1] and one of the most important determinants of attractiveness in humans.[2]

However, excessive or irrational concern with or preference for symmetry may also be indicative of psychopathology. For example, obsessions with symmetry and related compulsions, such as ordering and arranging, have received increased empirical attention in recent years. Analyses of obsessive-compulsive symptomatology in obsessive-compulsive disorder (OCD) have consistently identified a factor characterized by symmetry concerns and related rituals.[3,4] In OCD, symmetry obsessions are characterized by the need for things to be perfect, exact or "just right," symmetrical, or correctly aligned, and related compulsions include ordering and arranging, evening up or aligning things, and touching or tapping.

Symmetry symptoms have previously been found to occur more frequently in men and to be associated with earlier age of onset of OCD.[5,6] Symmetry in OCD has also been associated with poorer prognosis, including increased comorbidity with a range of psychiatric conditions, such as Tourette's disorder[4,5]; decreased level of functioning; and poorer response to treatment.[7,8] In a prospective follow-up study of treated OCD patients, symmetry/ordering was the only symptom dimension from the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) that was more common among those who attempted or committed suicide, and it was independently associated with suicidal behaviors.[9]

In humans, it has also been argued that symmetry or symmetry-related behaviors may have specific psychobiologic and evolutionary underpinnings.[10] Interestingly,

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familial OCD (compared to sporadic OCD) has also been found to be associated with increased compulsions, particularly ordering, i.e., one aspect of the symmetry symptom dimension.[11] Animal studies have indicated that the dopamine neurotransmitter system is involved in symmetry.[12] This is consistent with a range of data pointing to an important role for the dopamine system in OCD.[13] Alterations in the dopaminergic system may reflect the influence of particular environmental factors (e.g., exposure to stress or adversity)[14] or particular genetic factors (e.g., functional variants in the dopamine system).[15] However, although OCD is considered a polygenic disorder,[16] the particular association of symmetry-related symptomatology, early adversity, and selected polymorphisms in dopaminergic genes has, to our knowledge, not been investigated in this condition.

Here, we aimed to investigate the clinical and genetic associations of symmetry symptoms in OCD, with a particular focus on associations of these symptoms with early adversity and with variants in the dopamine system. We hypothesized that OCD patients with symmetry symptoms would have greater illness severity (i.e., increased OCD severity, psychiatric comorbidity and childhood trauma, and decreased level of functioning and longer duration of illness) and that there would be evidence for significant associations between symmetry and early adversity, and between symmetry and polymorphisms in candidate dopaminergic genes.

Materials and methods

Subjects

Four hundred and fifty-one patients with primary OCD (221 male; 230 female) took part in the study. All patients met DSM-IV-TR criteria for current OCD[17] on the Structured Clinical Interview for the Diagnosis of Axis I Disorders - Patient Version (SCID-I/P).[18] A psychologist, psychiatrist, or psychiatric nurse interviewed the participants. The exclusion criteria were history of psychosis, inadequate understanding of the goals and implications of study participation, and unwillingness to provide consent after being presented with the study information. The Ethics Committee of the University of Stellenbosch gave approval for the study to be conducted, and all participants gave informed written consent to participate after the risks and benefits of participation had been fully explained.

Data collection

Demographic data (including age and gender) were collated. The nature, prominence, and severity of OCD symptoms were assessed using the DY-BOCS and/or the Yale-Brown Obsessive-Compulsive Checklist and Severity Scale (Y-BOCS).[19] Data collection at our site has been ongoing for a number of years. Initially, before the DY-BOCS was available, the Y-BOCS checklist was used to assess for the presence/absence of specific symptoms and whether these particular symptoms were primary. More recently, the DY-BOCS was added to the assessment battery, which led to a situation in which we have Y-BOCS data for some patients, DY-BOCS data for others, and data from both scales for the rest.

The SCID-I/P was used to assess for DSM axis I disorders,[18] and the SCID-II/P to assess for selected personality disorders. The Structured Clinical Interview for the Diagnosis of OCD Spectrum Disorders (SCID-OCSD) was administered to assess for OCD-related disorders.[20]

Age of onset and duration of OCD were noted. Patients also completed a disability profile (DP),[21] which was used to assess lifetime impairment in eight domains (alpha coefficients: 0.87 for current rating, 0.90 for lifetime rating) due to OCD. Each item is rated separately for current and for lifetime disability on a five-point, descriptively anchored scale ranging from 0 (no impairment) to 4 (severe impairment).

The Childhood Trauma Questionnaire (CTQ), a self-report scale used to assess a broad range of traumatic experiences in childhood,[22] was completed by all participants. This questionnaire comprises 28 items that fall into five categories/subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The reliability and validity of the CTQ have been well researched.[22]

Genotyping

DNA, extracted from venous blood (10-30 mL) in a Caucasian subset (n=343) of participants with current primary symmetry-related obsessions and/or compulsions (n=156 [45.5%]) and those without (n=187 [54.5%]), was genotyped to investigate polymorphisms in key dopaminergic genes. For the purposes of this study, South African Caucasians were classified as those participants who were white and had self-reported home languages of English and/or Afrikaans. The polymorphisms investigated were: a 48 base-pair (bp) variable number of tandem repeats (VNTR) in the third exon of the dopamine receptor 4 (*DRD4*), a 40-bp VNTR in the 3′ untranslated region of the dopamine transporter (*DAT*), the catechol-O-methyl transferase (*COMT*) *Val158Met* polymorphism, the monoamine oxidase A (*MAOA*) *C1460T/EcoRV* polymorphism, the *DRD3* Ser9Gly polymorphism (rs6280), the rs4532 polymorphism in the dopamine receptor 1 (*DRD1*) gene, and the *Taq*I A (rs1800497) polymorphism located downstream of the *DRD2* gene, within the gene encoding ankyrin repeat and kinase containing domain 1 (*ANKK1*). There is evidence to suggest that these genes are directly involved with dopamine regulation in multiple brain regions, and are implicated in the pathogenesis of OCD.[16] Previously described genotyping protocols[23,24] were followed.

Statistical analysis

The sample was divided into two groups: those with primary symmetry concerns and/or compulsions and those without these symptoms. To determine whether symmetry and related symptomatology were primary, we employed the following method: Four Y-BOCS items specifically refer to this symptom dimension, and those patients who indicated that these symptoms were primary were allocated to the group with primary symmetry symptomatology. In terms of

Table 1 Demographic data in OCD patients with and without primary symmetry symptomatology

Variable	OCD with symmetry-related symptoms (n=210)	OCD without symmetry-related symptoms (n=241)	Statistics	p-value
Gender				
Male	96 (45.7)	125 (51.9)	$\chi^2 = 1.701$	NS
Female	114 (54.3)	116 (48.1)		
Age (years)	34.5±13.0	29.7±12.2	F = 1.395	$p < 0.01$*

Data presented as n (%) or mean ± standard deviation.
NS = not significant; OCD = obsessive-compulsive disorder.
* Mann-Whitney *U* test.

the DY-BOCS, symmetry symptoms were considered primary if the chronological severity item on the scale was marked as either 1 or 2, indicating that the patient considered this particular symptom dimension the most (or second most) prominent of all their OCD symptoms.

The 40-bp VNTR in *DAT* and 48-bp VNTR in *DRD4* presented a unique challenge within the statistical analyses due to the possibly of more than three genotype options within the cohort. All possible combinations were considered (*DRD4* = 13 possible combinations; *DAT* = six possible combinations). This challenge was addressed by the Multiple Testing Procedure in SAS, which handles data arising from a multivariate one-way analysis of variance (ANOVA) model with discrete response variables. The requested adjusted p-values are based on the idea of Fisher's combination test. This Fisher's combination option requests adjusted p-values by using closed tests, based on the idea of Fisher's combination test (a joint test of any set of *S* hypotheses with p-values using the chi-square statistic with 2*S* degrees of freedom). Furthermore, as the *MAOA* gene lies on the X chromosome, genetic association analyses for polymorphisms within this gene were performed on a stratified cohort (males and females separately).

It has been argued that correction for population structure is necessary, given that spurious association may result if the genetic background of the subpopulations comprising the sample under investigation differ.[25] The *MAOA* and *DAT* genes necessitated adjustment for home language with the group comparisons (previous work by our group found that using language as a proxy for population structure served well in statistically correcting for this factor, if applicable[26]).

Clinical and genetic data were compared between patients with primary symmetry concerns and/or compulsions and those without these symptoms by using ANOVAs and chi-square tests as appropriate.

P-values < 0.05 were considered significant.

Results

Demographics

There were 451 participants with a primary diagnosis of OCD; 210 (46.6%) of those reported current primary symmetry obsessions and related compulsions, including ordering, counting and arranging, and 241 (53.4%) were free of these symptoms. The two groups were similar in gender distribution but differed significantly in terms of their age at the time of assessment (Table 1). Patients reporting current primary symmetry-related symptoms were significantly older than those without symmetry concerns.

Clinical characteristics

The two groups differed significantly on a number of clinical aspects (Table 2). Those with symmetry symptomatology had significantly higher OCD severity scores ($p = 0.01$) and reported longer illness duration ($p < 0.01$) than those without.

Presence of OCD symmetry symptomatology was also significantly associated with lifetime comorbid panic disorder, posttraumatic stress disorder (PTSD), and obsessive-compulsive personality disorder (OCPD) ($p < 0.01$; Table 3).

Genetics

COMT (rs4680), *DRD1* (rs4532), *DRD2/ANKK1* (rs1800497), *DRD3* (rs6280), the 40-bp (*DAT*) and 48-bp (*DRD4*) VNTRs, and *MAOA* (rs1137070) were assessed for significant associations with primary symmetry symptoms reported by Caucasian patients with OCD.

In this Caucasian subset, genotype frequency differed significantly between OCD patients with primary symmetry symptomatology and those without, for *ANKK1* rs1800497,

Table 2 Clinical data in OCD patients with and without primary symmetry symptomatology

Variable	OCD with symmetry-related symptoms (n=210)	OCD without symmetry-related symptoms (n=241)	p-value*
Age at OCD onset (years)	16.9±10.8	16.6±8.8	NS
OCD severity (Y-BOCS total)	21±7	19.2±6.9	p = 0.01
DP total	11.1±5.3	10.5±5.3	NS
CTQ total	42.4±16.9	41.6±14.7	NS
Illness duration (years)	17.5±12	13.01±11.5	$p < 0.01$

Data presented as mean ± standard deviation.
CTQ = Childhood Trauma Questionnaire; DP = disability profile; NS = not significant; OCD = obsessive-compulsive disorder; Y-BOCS = Yale-Brown Obsessive-Compulsive Checklist and Severity Scale.
* Mann-Whitney *U* test.

Table 3 Lifetime comorbidity data in OCD patients with and without primary symmetry symptomatology

Comorbid disorder	With symmetry-related symptoms (n=208, except where indicated)	Without symmetry-related symptoms (n=238, except where indicated)	Statistics
Major depressive disorder	127 (61.1)	159 (66.8)	$\chi^2_{(1)} = 1.593$, p = NS
Dysthymic disorder	40 (19.2)	40 (16.8)	$\chi^2_{(1)} = 0.442$, p = NS
Bipolar disorder	8 (3.8)	7 (2.9)	$\chi^2_{(1)} = 0.279$, p = NS
Panic disorder (with/without agoraphobia)	30 (14.4)	15 (6.3)	$\chi^2_{(1)} = 8.138$, p = 0.004
Social anxiety disorder	25 (12)	16 (6.7)	$\chi^2_{(1)} = 3.734$, p = NS
Specific phobia	24 (11.5)	34 (14.3)	$\chi^2_{(1)} = 0.745$, p = NS
Generalized anxiety disorder	25 (12)	25 (10.5)	$\chi^2_{(1)} = 0.255$, p = NS
Posttraumatic stress disorder	15 (7.2)	4 (1.7)	$\chi^2_{(1)} = 8.706$, p = 0.003
Alcohol abuse	15 (7.2)	11 (4.6)	$\chi^2_{(1)} = 1.354$, p = NS
Alcohol dependence	8 (3.8)	4 (1.7)	$\chi^2_{(1)} = 2.006$, p = NS
Substance abuse	6 (2,9)	5 (2.1)	$\chi^2_{(1)} = 0.283$, p = NS
Substance dependence	4 (1.9)	7 (2.9)	$\chi^2_{(1)} = 0.486$, p = NS
Hypochondriasis	6 (2.9)	4 (1.7)	$\chi^2_{(1)} = 0.734$, p = NS
Body dysmorphic disorder	15 (7.2)	15 (6.3)	$\chi^2_{(1)} = 0.146$, p = NS
Anorexia nervosa	11 (5.3)	12 (5)	$\chi^2_{(1)} = 0.014$, p = NS
Bulimia nervosa	12 (5.8)	12 (5)	$\chi^2_{(1)} = 0.115$, p = NS
Binge-eating disorder	5 (2.4)	3 (1.3)	$\chi^2_{(1)} = 0.826$, p = NS
Tourette's disorder	4 (1.9)	5 (2.1)	$\chi^2_{(1)} = 0.018$, p = NS
Tic disorder	20 of 204 (9.8)	26 of 231 (11.3)	$\chi^2_{(1)} = 0.242$, p = NS
Intermittent explosive disorder	28 (13.5)	24 (10.1)	$\chi^2_{(1)} = 1.226$, p = NS
Kleptomania	6 (2.9)	8 (3.4)	$\chi^2_{(1)} = 0.083$, p = NS
Trichotillomania (hair-pulling disorder)	14 (6.7)	9 (3.8)	$\chi^2_{(1)} = 1.976$, p = NS
Non-suicidal self-injury	19 (9.1)	24 (10.1)	$\chi^2_{(1)} = 0.115$, p = NS
Compulsive shopping	11 (5.3)	10 (4.2)	$\chi^2_{(1)} = 0.291$, p = NS
Hypersexuality disorder	5 (2.4)	8 (3.4)	$\chi^2_{(1)} = 0.364$, p = NS
Stereotypic movement disorder	2 of 199 (1)	3 of 227 (1.3)	$\chi^2_{(1)} = 0.092$, p = NS
Borderline personality disorder	42 of 194 (21.6)	36 of 222 (16.2)	$\chi^2_{(1)} = 2.002$, p = NS
Obsessive-compulsive personality disorder	80 of 197 (40.6)	34 of 223 (15.2)	$\chi^2_{(1)} = 34.592$, $p < 0.001$
Avoidant personality disorder	36 of 194 (18.6)	33 of 222 (14.9)	$\chi^2_{(1)} = 1.018$, p = NS
Schizotypal personality disorder	2 of 194 (1)	6 of 221 (2.7)	$\chi^2_{(1)} = 1.636$, p = NS

Data presented as n (%).
NS = not significant; OCD = obsessive-compulsive disorder.

previously known as the *DRD2 Taq*I A polymorphism (χ^2 = 7.296; p = 0.026), with more OCD patients with symmetry symptoms being homozygous for the *A2* (*CC*) genotype. Furthermore, the frequency of the *A2* (*C*) alleles was significantly increased in patients with primary symmetry symptoms compared to those without (χ^2 = 4.1; p = 0.043) (Table 4).

We found no statistically significant associations of *COMT* (rs4680), *DRD1* (rs4532), or *DRD3* (rs6280) with symmetry symptomatology in our sample. Similarly, symmetry symptoms were not significantly associated with *MAOA* (rs1137070) (stratified for gender) (Table 5).

Statistical significance was not observed for either the 40-bp (*DAT*) or the 48-bp (*DRD4*) VNTRs (p = 0.65 and 0.19, respectively) (Table 6). Due to the multiple allelic combinations observed for the VNTRs, multiple testing was corrected for and permutation testing performed. The results indicate that none of the observed allelic combinations were associated with symmetry symptomatology in patients with OCD.

Population substructure using language as a proxy did not significantly influence the results reported herein.

Assuming a maximum false-positive of 3 for the polymorphisms investigated for a relative genetic risk of

Table 4 Allele frequencies and genotype distribution of *ANKK1* rs1800497 (*DRD2 Taq*I A polymorphism) in a Caucasian subset of OCD patients with and without primary symmetry symptomatology

		Allele frequencies			Genotype distribution			
	n	*A1* (*T* allele)	*A2* (*C* allele)	p-value	*A1A1* (*T/T*)	*A1A2* (*T/C*)	*A2A2* (*C/C*)	p-value
OCD with symmetry-related symptoms	116	35 (15.09)	197 (84.91)	$\chi^2 = 4.1$, p = 0.043	1 (0.41)	33 (13.52)	82 (33.61)	$\chi^2 = 7.296$, p = 0.026
OCD without symmetry-related symptoms	128	57 (22.27)	199 (77.73)		9 (3.69)	39 (15.98)	80 (32.79)	

Data presented as n (%).
OCD = obsessive-compulsive disorder.

Table 5 Associations of dopaminergic genes with symmetry in OCD (excluding *ANKK1* rs1800497)

Gene	Polymorphism	p-value
COMT	rs4680	0.70
MAOA	rs1137070	Males: 0.58 Females: 0.16
DAT	40bp VNTR	0.19
DRD1	rs4532	0.95
DRD3	rs6280	0.85
DRD4	48bp VNTR	0.65

bp = base pair; OCD = obsessive-compulsive disorder; VNTR = variable number tandem repeat.

1.2, depending on the disease allele frequencies, power could vary greatly. In terms of *ANKK1* rs1800497 specifically, power would range between 74 and 90% for incidence rates of 36-50%, respectively. With a 46.5% primary symmetry incidence rate in the current cohort, an adequate percentage of 87% power was theorized. This holds true for common polymorphisms of MAF $\geqslant$ 0.2.[27]

Discussion

Just less than half of the study sample (46.6%) reported primary symmetry-related obsessions and compulsions. This is consistent with previous work, which has described symmetry obsessions in 36 to 50% in adults with OCD.[28,29] OCD patients with primary symmetry-related symptoms had significantly higher OCD severity scores, longer illness duration, and increased psychiatric comorbidity - but not increased childhood trauma or lower level of functioning - compared to those without these symptoms, suggesting that presence of primary symmetry-related symptoms may represent a marker of severity in OCD. Further work is needed to determine whether similar relationships also hold in other psychiatric disorders, such as body dysmorphic disorder (BDD), which are often characterized by symmetry symptoms.[30]

Arguably, an attempt at a detailed analysis of the relation between symmetry and any particular (comorbid) disorder would be going beyond the data at hand. Nevertheless, it is important to note that it is very common for patients with OCD to present with other psychiatric disorders. We found increased rates of OCPD in the cohort with primary symmetry-related symptoms. This condition is characterized by a chronic maladaptive pattern of excessive perfectionism and a preoccupation with orderliness and detail - traits which closely reflect the so-called symmetry/ordering/counting/arranging symptom dimension in OCD. We also observed a significant association between primary symmetry symptomatology and comorbid PTSD, an interesting finding given reports of a link between stress and dopamine,[14] as noted earlier.

In terms of psychobiological underpinnings, we expected to find links between some of the selected dopaminergic genes and symmetry in OCD, given the evidence from some human and animal model studies. Specifically, one study found a significant association between the symmetry symptom dimension and the *2R* allele of the *DRD4* VNTR polymorphism, subsequently suggesting that this symptom dimension may represent a more homogeneous subtype of OCD with a genetic etiology.[31] This particular finding was not replicated here. We found that the genotype frequency of the *ANKK1* rs1800497 polymorphism differed significantly between the comparison groups, with more OCD patients with symmetry symptoms being homozygous for the *A2A2* (*CC*) genotype. *ANKK1* rs1800497 is a restriction fragment length polymorphism of *DRD2*, comprising two alleles, which have historically been referred to as *A1* (*T* allele) and *A2* (*C* allele).[32-34]

A number of studies have indicated that this single-nucleotide polymorphism is associated with altered *DRD2*

Table 6 Permutation correcting for multiple testing associated with multiallelic VNTR combinations

Gene	Polymorphism	Variable*	p-value	
			Raw	Permutation
DAT	40bp VNTR	A9A9	0.172	0.510
		A9A10	0.642	0.987
		A10A10	0.826	0.999
		A10A11	0.132	0.437
		A9A11	0.254	0.729
		A2A10	1	1
DRD4	48bp VNTR	A7A7	0.334	0.944
		A4A7	0.209	0.818
		A4A4	0.315	0.904
		A2A2	1	1
		A2A4	1	1
		A3A4	0.295	0.898
		A3A3	1	1
		A4A5	0.593	1
		A4A6	0.629	1
		A3A7	1	1
		A5A5	1	1
		A3A6	0.503	0.999
		A2A7	1	1

VNTR = variable number tandem repeat.
* Variable refers to the allelic combination being assessed, where A is the designated allele and the subsequent numeric value is the number of repeats of that allele.

expression and has functional effects on dopamine receptor density.[35] Data from the HapMap project have also suggested that the *Taq1*A variant is in linkage disequilibrium with other variants in the *DRD2* gene, but not with variants in the *ANKK1* gene.[34] Since the *A1* (ancestral) allele of the *ANKK1* rs1800497 polymorphism has been found to be associated with a variety of addictive, impulsive, and compulsive disorders, such as alcoholism, drug abuse, smoking, obesity, and compulsive gambling, as well as with several personality disorders,[36] the association of the *A2A2* genotype and *A2* allele (the newly evolved variant) found herein was arguably unexpected. On the other hand, the literature has also emphasized that compulsive and impulsive disorders may at times have divergent underlying neurobiology. The new *A2* variant is associated with increased *D2* density in the striatum. (Speculatively, the new *A2* variant is associated with greater reward from symmetry-related stimuli, while the ancient *A1* variant is associated with greater reward from impulsive behaviors; further work is needed, however, to understand the functional psychobiology of gene variants in *ANKK1* rs1800497.)

To our knowledge, only three previous studies have examined the association between the *DRD2 Taq*I A system and OCD, and none of those found a significant association with OCD in general.[37-39] However, two of those studies found an association with a subgroup of OCD patients, i.e., OCD with tics, and OCD with an early age of onset: Nicolini et al.[38,39] observed a higher frequency of the *ANKK1* rs1800497 *A2* alleles and more individuals homozygous for *A2A2* in a subgroup with comorbid tics; Denys et al.[40] found an association between the *A2A2* genotype in patients with an early onset of OCD, and when their sample was stratified by gender, there was a trend towards significance for the *A2A2* genotype ($p = 0.049$), and a higher frequency of the *A2* alleles in male OCD patients compared to male controls. There is certainly a relationship between the tic subtype of OCD, early onset of OCD, and symmetry symptoms, as demonstrated by our findings. Thus, it is also possible that the *ANKK1* rs1800497 (new) variant is associated with risk of this phenotype – perhaps reflecting increased striatal dopaminergic activity.

Considering the link between symmetry symptoms and OCD severity noted earlier, and that human and animal studies both confirm the involvement of dopamine circuitry in OCD, it is interesting that treatment-resistant OCD specifically may exhibit improved response following adjunctive treatment with a D_2 receptor antagonist.[41] The above-mentioned relationship between primary symmetry symptomatology and comorbid PTSD may also have a connection with dopamine, especially since altered dopaminergic activity has been suggested to compromise the ability to develop effective coping strategies following aversive situations in an animal model.[42]

Several limitations should be acknowledged. Other genetic variants, or interactions with others, may play a role. These findings should be considered preliminary, as the numbers of patients for whom we had genetic data were small, resulting in relatively little power to detect group differences. In addition, future investigations should take into account epigenetic effects, which impact the expression of genes without altering the primary DNA sequence. Indeed, a potentially complementary line of research implicates *DRD2* in gene-environment correlations and interactions, in addition to its influence on the way in which symptoms present.[43] Nevertheless, one strength is that this was the first study to examine both the demographic/clinical and genetic correlates of primary symmetry symptomatology in OCD.

In conclusion, our findings replicate previous studies that suggested that symmetry symptoms are very common in OCD, have some distinct clinical features, and may represent a marker of OCD severity. However, the clinical associations observed, in combination with the significant association found with the *DRD2/ANKK1* rs1800497 *A2* polymorphism, suggest that primary symmetry obsessions and related compulsions may also represent a distinctive clinical and psychobiological profile in OCD. These are important findings, and may have clinical utility. Follow-up of associations between symmetry symptoms in OCD and functional gene variants in the dopaminergic system (and other possibly involved systems, e.g., the serotonergic and glutamatergic systems), in a larger sample to increase statistical power, is warranted.

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Disclosure

The authors report no conflicts of interest.

References

1 Grammer K, Thornhill R. Human (Homo sapiens) facial attractiveness and sexual selection: the role of symmetry and averageness. J Comp Psychol. 1994;108:233-42.
2 Bashour M. History and current concepts in the analysis of facial attractiveness. Plast Reconstr Surg. 2006;118:741-56.
3 Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C, Leckman JF. Meta-analysis of the symptom structure of obsessive-compulsive disorder. Am J Psychiatry. 2008;165:1532-42.
4 Lochner C, Hemmings SM, Kinnear CJ, Nel D, Hemmings SM, Seedat S, et al. Cluster analysis of obsessive-compulsive symptomatology: identifying obsessive-compulsive disorder subtypes. Isr J Psychiatry Relat Sci. 2008;45:164-76.
5 Hasler G, LaSalle-Ricci VH, Ronquillo JG, Crawley SA, Cochran LW, Kazuba D, et al. Obsessive-compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. Psychiatry Res. 2005;135:121-32.
6 Kichuk SA, Torres AR, Fontenelle LF, Rosario MC, Shavitt RG, Miguel EC, et al. Symptom dimensions are associated with age of onset and clinical course of obsessive-compulsive disorder. Prog Neuropsychopharmacol. Biol Psychiatry. 2013;44:233-9.
7 Stein DJ, Andersen EW, Overo KF. Response of symptom dimensions in obsessive-compulsive disorder to treatment with citalopram or placebo. Rev Bras Psiquiatr. 2007;29:303-7.
8 Stein DJ, Carey PD, Lochner C, Seedat S, Fineberg N, Andersen EW. Escitalopram in obsessive-compulsive disorder: response of symptom dimensions to pharmacotherapy. CNS Spectr. 2008;13:492-8.
9 Alonso P, Segalas C, Real E, Pertusa A, Labad J, Jimenez-Murcia S, et al. Suicide in patients treated for obsessive-compulsive disorder: a prospective follow-up study. J Affect Disord. 2010;124:300-8.

10 Stein DJ, Carey PD, Warwick J. Beauty and the beast: psychobiologic and evolutionary perspectives on body dysmorphic disorder. CNS Spectr. 2006;11:419-22.
11 Viswanath B, Narayanaswamy JC, Cherian AV, Reddy YC, Math SB. Is familial obsessive-compulsive disorder different from sporadic obsessive-compulsive disorder? A comparison of clinical characteristics, comorbidity and treatment response. Psychopathology. 2011;44:83-9.
12 Hoffman KL, Rueda Morales RI. D1 and D2 dopamine receptor antagonists decrease behavioral bout duration, without altering the bout's repeated behavioral components, in a naturalistic model of repetitive and compulsive behavior. Behav Brain Res. 2012;230:1-10.
13 Koo MS, Kim EJ, Roh D, Kim CH. Role of dopamine in the pathophysiology and treatment of obsessive-compulsive disorder. Expert Rev Neurother. 2010;10:275-90.
14 Pani L, Porcella A, Gessa GL. The role of stress in the pathophysiology of the dopaminergic system. Mol Psychiatry. 2000;5:14-21.
15 Varga G, Szekely A, Sasvari-Szekely M. Candidate gene studies of dopaminergic and serotonergic polymorphisms. Neuropsychopharmacol Hung. 2011;13:93-101.
16 Taylor S. Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol Psychiatry. 2013;18:799-805.
17 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Arlington: American Psychiatric Publishing; 2000.
18 First MB, Spitzer RL, Gobbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders. Patient Edition (SCID-I/P, Version 2.0, 8/98 revision). New York: New York State Psychiatric Institute, Biometrics Research Department; 1998.
19 Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46:1006-11.
20 du Toit PL, van Kradenburg J, Niehaus D, Stein DJ. Comparison of obsessive-compulsive disorder patients with and without comorbid putative obsessive-compulsive spectrum disorders using a structured clinical interview. Compr Psychiatry. 2001;42:291-300.
21 Schneier FR, Heckelman LR, Garfinkel R, Campeas R, Fallon BA, Gitow A, et al. Functional impairment in social phobia. J Clin Psychiatry. 1994;55:322-31.
22 Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wentzel K, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry. 1994;151:1132-6.
23 Hemmings SM, Kinnear CJ, Niehaus DJ, Moolman-Smook JC, Lochner C, Knowles JA, et al. Investigating the role of dopaminergic and serotonergic candidate genes in obsessive-compulsive disorder. Eur Neuropsychopharmacol. 2003;13:93-8.
24 Niehaus DJ, Kinnear CJ, Corfield VA, du Toit PL, van Kradenburg J, Moolman-Smook JC, et al. Association between a catechol-o-methyltransferase polymorphism and obsessive-compulsive disorder in the Afrikaner population. J Affect Disord. 2001;65:61-5.
25 Astle W, Balding DJ. Population structure and cryptic relatedness in genetic association studies. Statist Sci. 2009;24:451-71.
26 Hemmings SM, Lochner C, van der Merwe L, Cath DC, Seedat S, Stein DJ. BDNF Val66Met modifies the risk of childhood trauma on obsessive-compulsive disorder. J Psychiatr Res. 2013;47:1857-63.
27 Skol AD, Scott LJ, Abecasis GR, Boehnke M. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet. 2006;38:209-13.
28 Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. Am J Psychiatry. 1999;156:1409-16.
29 Pinto A, Greenberg BD, Grados MA, Bienvenu OJ 3rd, Samuels JF, Murphy DL, et al. Further development of YBOCS dimensions in the OCD Collaborative Genetics study: symptoms vs. categories. Psychiatry Res. 2008;160:83-93.
30 Hart AS, Phillips KA. Symmetry concerns as a symptom of Body Dysmorphic Disorder. J Obsessive Compuls Relat Disord. 2013;2: 292-8.
31 Taj M J RJ, Viswanath B, Purushottam M, Kandavel T, Janardhan Reddy YC, Jain S. DRD4 gene and obsessive compulsive disorder: do symptom dimensions have specific genetic correlates? Prog Neuropsychopharmacol Biol Psychiatry. 2013;41:18-23.
32 Eisenberg DT, Mackillop J, Modi M, Beauchemin J, Dang D, Lisman SA, et al. Examining impulsivity as an endophenotype using a behavioral approach: a DRD2 TaqI A and DRD4 48-bp VNTR association study. Behav Brain Funct. 2007;3:2-2.
33 Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat. 2004;23:540-5.
34 Savitz J, Hodgkinson CA, Martin-Soelch C, Shen PH, Szczepanik J, Nugent AC, et al. DRD2/ANKK1 Taq1A polymorphism (rs1800497) has opposing effects on D2/3 receptor binding in healthy controls and patients with major depressive disorder. Int J Neuropsychopharmacol. 2013;16:2095-101.
35 Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, et al. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics. 1997;7:479-84.
36 Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res. 2000;126:325-41.
37 Billett EA, Richter MA, Sam F, Swinson RP, Dai XY, King N, et al. Investigation of dopamine system genes in obsessive-compulsive disorder. Psychiatr Genet. 1998;8:163-9.
38 Nicolini H, Cruz C, Camarena B, Orozco B, Kennedy JL, King N, et al. DRD2, DRD3 and 5HT2A receptor genes polymorphisms in obsessive-compulsive disorder. Mol Psychiatry. 1996;1:461-5.
39 Nicolini H, Cruz C, Paez F, Camarena B. [Dopamine D2 and D4 receptor genes distinguish the clinical presence of tics in obsessive-compulsive disorder]. Gac Med Mex. 1998;134:521-7.
40 Denys D, Van Nieuwerburgh F, Deforce D, Westenberg H. Association between the dopamine D2 receptor TaqI A2 allele and low activity COMT allele with obsessive-compulsive disorder in males. Eur Neuropsychopharmacol. 2006;16:446-50.
41 Denys D. Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr Clin North Am. 2006;29:553-84, xi.
42 Harvey BH, Brand L, Jeeva Z, Stein DJ. Cortical/hippocampal monoamines, HPA-axis changes and aversive behavior following stress and restress in an animal model of post-traumatic stress disorder. Physiol Behav. 2006;87:881-90.
43 Hayden EP, Klein DN, Dougherty LR, Olino TM, Laptook RS, Dyson MW, et al. The dopamine D2 receptor gene and depressive and anxious symptoms in childhood: associations and evidence for gene-environment correlation and gene-environment interaction. Psychiatr Genet. 2010;20:304-10.