RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Prevalence and Heritability of Obsessive-Compulsive Spectrum and Anxiety Disorder Symptoms: A Survey of the Australian Twin Registry

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Manuscript Received: 29 October 2013; Manuscript Accepted: 26 March 2014

While past twin studies indicate moderate levels of heritability of "obsessive-compulsive related" and anxiety disorder symptoms, no single study has reported such estimates in the same twin population nor examined potential genetic sex differences. We assessed symptoms of obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, hypochondriasis, panic disorder, social phobia and generalized anxiety disorder in 2,495 adult twins (1,468 female). Prevalence estimates for the corresponding symptom measures were determined using empirically derived cut-off scores. Twin resemblance was assessed by Pearson correlations and biometrical model-fitting analyses, incorporating sex-specific effects, using OpenMx. Prevalence estimates ranged from 1.6% in the symptoms of generalized anxiety to 16.9% for social phobia. Female twins demonstrated significantly higher prevalence rates across all domains with the exception of obsessive-compulsive symptoms. Additive genetic factors accounted for a moderate proportion of the total liability to each symptom domain. Evidence suggesting qualitative

How to Cite this Article:
López-Solà C, Fontenelle LF, Alonso P, Cuadras D, Foley D, Pantelis C, Pujol J, Yücel M, Cardoner N, Soriano-Mas C, Menchón JM, Harrison BJ. 2014. Prevalence and Heritability of Obsessive-Compulsive Spectrum and Anxiety Disorder Symptoms: A Survey of the Australian Twin Registry.
Am J Med Genet Part B 165B:314–325.

Conflict of interest: None.
Grant sponsor: Early Career Researcher Grant from The University of Melbourne; Grant sponsor: National Health and Medical Research Council of Australia (NHMRC) Clinical Career Development Fellowship; Grant number: 628509; Grant sponsor: Spanish Ministry of Education, Culture and Sport; Grant number: FPU12/01636; Grant sponsor: 'Miguel Servet' contract from the Carlos III Health Institute; Grant number: CP10/00604; Grant sponsor: NHMRC Senior Principal Research Fellowship; Grant number: 628386; Grant sponsor: NARSAD Distinguished Investigator Award; Grant sponsor: NHMRC Senior Research Fellowship; Grant number: 1021973.
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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 23 April 2014
DOI 10.1002/ajmg.b.32233

genetic sex differences (i.e., distinct genetic influences between genders) was observed for body dysmorphic concern and panic symptoms, while quantitative differences were observed for hoarding and social phobia symptoms, indicating stronger heritability in females. Novel findings in this study include the observation of probable genetic sex differences in liability towards hoarding symptoms and dysmorphic concern, as well as the lack of such differences in hypochondriasis. The trend towards qualitative sex differences in panic symptoms has some intuitive appeal with regard to biological-experimental models of panic.

Key words: obsessive-compulsive related disorders; anxiety disorders; twins; genetic sex differences; heritability

INTRODUCTION

Introduction of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has seen obsessive-compulsive disorder (OCD) reclassified from the anxiety disorders category into a new grouping of "OC-related" disorders, including body dysmorphic disorder, trichotillomania (hair-pulling disorder); as well as excoriation (skin picking) disorder and hoarding disorder as a new diagnosis. Separately, each of these disorders appears to have a clear familial aggregation [Bienvenu et al., 2000; Hettema et al., 2001; Chacon et al., 2007; Pertusa et al., 2008] as well as a higher prevalence rates in females—at least in relation to the anxiety disorders category. Much less is known about the influence of gender on the prevalence and heritability of OC-related disorders and whether there may exist potential genetic sex differences in terms of current estimated heritability rates. Because of the historical link between OCD and other anxiety disorders, there are actually very few studies to have assessed both categories of disorders in the same population at the same period of time. Epidemiological twin studies represent one such example, whereby the majority of published studies correspond to either the former (DSM-IV) conceptualization of anxiety disorders or the recently adopted conceptualization of "OC-related disorders" [Monzani et al., 2014]. Given the ongoing debate that surrounds the DSM-5 revisions, there appears to be merit in the completion of studies that assess both groups of disorders in the same population.

Twin studies represent an important research platform in psychiatry that allows estimation of the relative importance of genetic (i.e., heritable) and environmental influences on complex traits [Neale and Cardon, 1992]. Previous twin studies of anxiety symptoms and disorders have confirmed that additive genetic risk factors are important to their etiology with the estimated heritability of anxiety disorders ranging between 23% and 40% [Hettema et al., 2001; Mosing et al., 2009; Tambs et al., 2009]. With regard to OCD, the heritability of diagnosable cases has been estimated at 29% [Tambs et al., 2009], with higher rates (48%) estimated in relation to the experience of obsessive-compulsive symptoms [Clifford et al., 1984; Iervolino et al., 2011]. In the latter instance, the heritability of obsessive-compulsive symptoms has been reported as stable over time and mostly equivalent across genders in non-clinical samples [van Grootheest et al., 2009]. Regarding "OC-related disorders," heritability rates have also been estimated for compulsive hoarding symptoms (50%), body dysmorphic concern (44%), and skin picking (40%). This latter evidence has been marshalled from a single study of adult female twins from the "TwinsUK" registry [Iervolino et al., 2009; Monzani et al., 2012a,b].

To extend such recent findings, we performed the current study to compare prevalence and heritability rates for OC-related and anxiety disorder symptoms in an adult twin population, including male and female twin pair combinations, and with the intention of testing the influence of gender on estimated heritability. While the "TwinsUK" sample included females twins aged up to 86 years, we restricted the recruitment of twins to between 18 and 45 years; that is, approximating the age range at which the onset of these disorders is most prevalent in the general population [Kessler et al., 2012]. We also extended the current survey to examine hypochondriasis symptoms given parallel debate regarding its optimal classification in relation to anxiety and OC-related disorders [Phillips et al., 2010]. Thus, the primary objective of the current study was to examine the prevalence and heritability of OC-related and anxiety disorder symptoms together in a twin population, as well as the potential influence of genetic sex differences in explaining these heritability rates.

MATERIALS AND METHODS

Participants

Twins were recruited from the Australian Twin Registry (ATR)—a large national voluntary twin registry [overviewed in Hopper et al., 2013]. A total of 6,950 participants (3,475 twin pairs) were emailed by the ATR on our behalf to participate in an online survey of their experience of OC-related and anxiety symptoms. Twins were selected nation-wide according to age (18–45 years), zygosity, and gender combination, and a minimum duration of 6 months since having participated in an ATR-affiliated research study. Twin pairs were randomly selected to receive the study approach email—averaging 112 twin pairs/per week. After 2 weeks, non-responding twins were followed up with a reminder email, followed by a further telephone reminder 2 weeks later. A second phone follow up was performed for all remaining non-responders. This data collection phase ran for approximately 1 year between June 2011 and May 2012 with an overall response rate of 35.9%. We obtained a final sample of 2,495 twins (1,468 females and 1,027 males; Fig. 1).

Psychometric Measures

After providing informed consent and responding to a small number of sociodemographic factors twins completed the following self-report measures in this order: (1) Obsessive Compulsive Inventory-Revised (OCI-R) [Foa et al., 2002]; (2) Hoarding Rating Scale-Self Report (HRS-SR) [Tolin et al., 2010]; (3) Social Phobia Inventory (SPIN) [Connor et al., 2000]; (4) Anxiety Sensitivity Index (ASI) for panic symptoms [Reiss et al., 1986]; (5) Dysmorphic Concern Questionnaire (DCQ) [Oosthuizen et al., 1998]; (6) Skin-Picking Scale (SPS) [Keuthen et al., 2001]; (7) Whiteley Index (WI) to assess hypochondriasis symptoms [Pilowsky, 1967]; (8) Depression, Anxiety, and Stress Scale-21

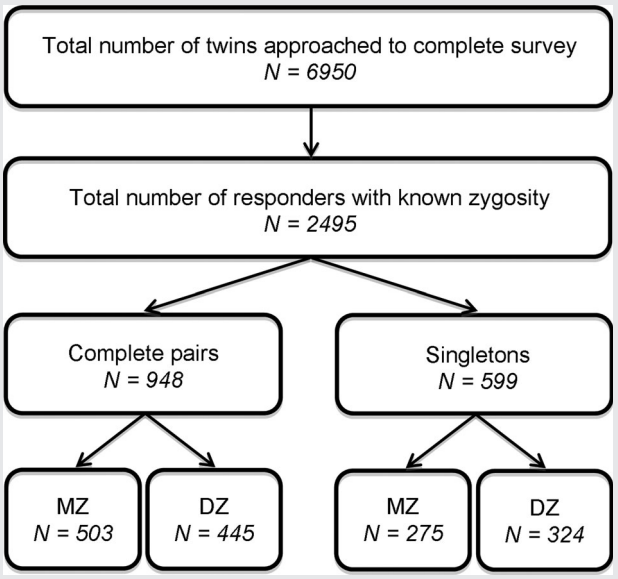

FIG. 1. Flow of the eligible twins through the study. The following zygosity and gender combinations were approached: 795 male monozygotic (MZ) pairs; 666 male dizygotic (DZ) pairs; 755 female MZ pairs; 666 female DZ pairs, and 583 male/female pairs.

(DASS-21) [Antony et al., 1998]; (9) Massachusetts General Hospital-Hair Pulling Scale (MGH-HPS) [O'Sullivan et al., 1995]. The DASS-21 "Stress" subscale was chosen as a proxy measure of generalized anxiety symptoms. This subscale measures persistent arousal, tension, irritability, and tendency to overreact to stressful events. Previous studies endorse its utility differentiating generalized anxiety disorder (GAD) from other anxiety disorders [Brown et al., 1992] as well as being strongly correlated with other measures of worry [Brown et al., 1995]. Cut-off scores were used to classify "clinical levels" of symptom ratings on each scale (see "supplementary online material"). The SPS was completed if participants first answered "yes" to one screening question: "Do you often feel the urge to pick your skin?" Similarly, four screening questions were completed for the MGH-HPS derived from the Structured Clinical Interview for DSM-Research Version (SCID-I/P). These screening questions were included in recognition of the likely low prevalence of symptoms and to reduce the general time burden of the survey as a whole.

Statistical Analysis

Estimation of prevalence. Prevalence estimates for each questionnaire were performed to quantify how many twins scored above the proposed cut-offs on each measure putatively distinguishing between "non-clinical" and "probable clinical" cases. A comparison of the prevalence rates between genders for each measure was evaluated using the Chi-square (χ^2) statistic.

Data normality. All questionnaire responses demonstrated varying degrees of skewness in their distributions. In order to improve the normality of our data Box–Cox transformations were applied [Box and Cox, 1964]. Box–Cox represents a family of power transformations that extend traditional methods in order to identify the optimal normalizing transformation regardless of whether the variable is negatively or positively skewed. In Box–Cox transformation [$y^{\lambda}_{t} = (y^{\lambda} - 1)/\lambda$] *lambda* ($\lambda$) can adopt an almost infinite number of values to calibrate a transformation to be maximally effective in moving a variable toward normality. We therefore estimated the best λ for each variable, separately. Only with regard to the DCQ was the estimated λ statistic equal to 0. In this case, a log transformation was applied to normalize the data. Maximum likelihood model fitting analyses were then conducted on transformed continuous variables.

Estimation of cross-twin–within-trait correlations. The Box–Cox transformed data was used to estimate cross twin—within-trait correlations. Comparing cross-twin (MZ vs. DZ) within-trait correlations provides a first impression of the contribution of genetic and environmental influences on a trait [Neale and Cardon, 1992]. To investigate sex differences, twin correlations were calculated separately for the five zygosity groups: MZ males, DZ males, MZ females, DZ females, and DZ opposite-sex.

Estimation of heritability. All twin analyses were carried out in both genders using the OpenMx package for RStudio ("http://openmx.psyc.virginia.edu/getOpenMx.R"). Structural equation modeling is an analysis tool where putative genetic and environmental influences are modelled to quantify their contribution to the estimated phenotypic variance for each trait measured in a population [Neale and Cardon, 1992]. An individual's phenotype is decomposed into A (*additive genetic factors*), C (*shared environment, shared by twins*), and E (*non-shared environment plus measurement error*). In addition, four models were performed to test for potential sex differences: "qualitative," "quantitative," "scalar," and "null" models. Qualitative sex differences refer to the estimation of distinct genetic and/or environmental influences for males and females, which is implied if the correlation for DZ opposite-sex is significantly less than the correlation for the same-sex DZ twins [Haworth et al., 2008]. In other words, is there evidence of distinct genetic and/or environmental influences on a given trait in males versus females? Quantitative sex differences, by comparison, refer to differences in the magnitude of common genetic and environmental influences when comparing MZ male and DZ male with that of MZ female and DZ female. In other words, is there evidence of stronger heritability of a given trait in males versus females?" In addition, we tested the fit of a "scalar model" whereby the genetic and environmental parameters are constrained to be equal in both sexes but allowing for a different variance in each trait for males and females. Finally, we refer to the "null model" as one that equates the genetic and environmental parameters and phenotypic variance to be equal in both sexes, allowing males and females to differ in their mean scores on each scale. Reduced qualitative and quantitative submodels, where the shared environmental parameter is removed, were tested to explain the observed data most parsimoniously, thus optimizing model fit. The qualitative ACE models were compared with a saturated model imposing equal means and variance restriction across twins and zygosity to maximize information. The Akaike information criterion (AIC) statistic [Akaike, 1987] [$\chi^2 - 2(df)$] and the difference in the χ^2 value relative to the chance in degrees of

freedom provided an indication of the models' goodness of fit [Neale and Cardon, 1992].

RESULTS

Sociodemographic Measures

Table I provides a comparison of the demographic composition of the MZ and DZ twin pair combinations. A total of 503 MZ and 445 DZ twin pairs as well as 275 MZ and 324 DZ singleton twins completed the survey (1,468 females and 1,027 males). The mean (SD) age was 34.5 (7.8) and 33.9 (8) years for MZ and DZ, respectively. With regard to demographic indices, no significant differences were observed between MZ and DZ twins (Table I).

Estimation of Prevalence

Table II reports the mean scores for each scale in the total sample and the number of twins scoring above the proposed cut-offs on each scale indicating probable "case level" symptoms. Across the entire sample, these prevalence estimates ranged from 1.6% in relation to GAD symptoms (DASS-Stress subscale) to 16.9% in social phobia symptoms. Female twins had a significantly higher prevalence than males across all scales, except for the OCI-R.

Because two cut-off scores have been proposed for the DCQ ($\geq$11 and $\geq$17) and DASS-21 (between 13 and 16, and $\geq$17) scales, we only report prevalence estimates for the highest proposed cut-offs in Table II in order to classify more clinically symptomatic levels. With regard to the DCQ, 8.8% of the entire sample (6.6% female and 2.2% male) scored above the lower proposed cut-off ($\geq$11) while almost 2% of the sample demonstrated probably case-level symptoms when using the higher cut-off ($\geq$17). With regard to the Stress subscale 5.2% (3.8% female and 1.4% male) reported severe symptoms of persistent arousal, tension and irritability (cut-off range 13–16), whereas only 1.6% of the sample reported extremely severe symptoms ($\geq$17) (Fig. 2).

Prevalence estimates for the SPS and MGH-HPS were not as well estimated compared to other measures, primarily due to the use of initial screening questions for these scales. With regard to SPS, only 52 twin pairs (33 MZ and 19 DZ) and 8 MZ and 4 DZ singleton twins screened positive and completed all items, whereas no complete pairs answered the full MGH-HPS. For the SPS, 24% of these participants scored above the proposed cut-off (17.8% females; 6.3% males). Due to the low response rate for skin picking and trichotillomania it was not possible to estimate their heritability in further analyses.

Estimation of Cross-Twin—Within-Trait Correlations

For all measures, cross-twin—within-trait Pearson's correlations for male and female twins were double in magnitude in the MZ compared to DZ pairs (Table III), consistent with a genetic influence across symptom domains. Correlations for opposite-sex DZ twins were similar for same-sex DZ twins in SPIN and

TABLE I. Demographic Characteristics of the Female and Male Twin Sample

Sociodemographic (N = 2,495 twins)	Monozygotic (N = 1,281)	Dizygotic (N = 1,214)	*t*-Student/χ^2 (*P*-value bilateral)
Gender			
Male/male	204 pairs/125 singleton	111 pairs/132 singleton	
Female/female	299 pairs/150 singleton	194 pairs/192 singleton	—
Male/female	—	140 pairs	
Age			
Mean (SD)	34.5 (7.8)	33.9 (8)	1.98 (0.05)
Marital status			
Married/partner (%)	44%	47%	3.15 (0.53)
Girlfriend/boyfriend (%)	12.1%	10.6%	
Divorced/separate (%)	33.7%	33.6%	
Single (%)	10.2%	8.6%	
Widowed (%)	0%	0.1%	
Education			
Primary/secondary school	59.1%	56.2%	3.97 (0.27)
TAFE qualification	28.1%	28.3%	
Undergraduate	7.8%	9.4%	
Post-graduate	4.9%	6.2%	
Employment			
Student (%)	43.6%	39.9%	7.12 (0.21)
Unemployed (%)	8.4%	7%	
Self-employed (%)	18%	19.1%	
Part/time employed (%)	12.5%	14.3%	
Full/time employed (%)	17.6%	19.7%	

OCD, obsessive-compulsive disorder; TAFE, technical and further education.

TABLE II. Means and Standard Deviation (SD) of the Total Scores in Each Scale By Sex and By Zygosity

	Mean (SD) total score				Prevalence						
	Sex		Zygosity		Total Sample (N = 2,495)		Female Twins (N = 1,468)		Male Twins (N = 1,027)		Compare between gender
Variables (cut-off)	Male	Female	MZ	DZ	N	%	N	%	N	%	χ^2 (*P*-value)
OCI-R (≥21)	8.3 (7.8)	8.8 (8.6)	8.6 (8.6)	8.6 (8)	218	8.7	139	9.5	79	7.7	2.4 (0.12)
HRS-RS (≥17)	2.7 (4)	2.8 (4.8)	2.7 (4.5)	2.9 (4.6)	64	2.6	48	3.3	16	1.6	7.1 (0.008)
DCQ (≥17)	3.6 (3.3)	4.9 (4.4)	4.2 (3.9)	4.5 (4.1)	47	1.9	41	2.8	6	0.6	15.95 (<0.001)
WI (≥8)	2.3 (2.4)	2.8 (2.7)	2.6 (2.7)	2.6 (2.6)	170	6.8	116	7.9	54	5.3	6.65 (0.01)
ASI (≥30)	7.3 (7.3)	9.1 (9.4)	8.3 (8.7)	8.5 (8.7)	87	3.5	69	4.7	18	1.8	15.6 (<0.001)
SPIN (≥21)	9.9 (9.7)	12.6 (12.1)	11.5 (11.5)	11.5 (10.9)	421	16.9	298	20.3	123	12	29.8 (<0.001)
DASS.Stress (≥17)	3.3 (3.6)	4.5 (4.3)	4.1 (4.2)	3.9 (3.9)	40	1.6	30	2	10	1	4.39 (0.04)

MZ, monozygotic; DZ, dizygotic; OCI-R, obsessive-compulsive inventory–revised; HRS-SR, hoarding rating scale-self report; DCQ, dysmorphic concern questionnaire; WI, Whiteley index; ASI, anxiety sensitivity index; SPIN, social phobia inventory; DASS.Stress, stress subscale of the depression, anxiety, and stress scale.
Prevalence for total sample and separated by gender of problematic symptoms based on empirically defined cut-off scores on each scale.

hypochondriasis. However, opposite-sex DZ twins correlations were lower compare to same-sex correlations for panic (ASI), obsessive-compulsive (OCI-R), generalized anxiety (Stress subscale), dysmorphic concern (DCQ), and hoarding (HRS-SR) symptoms, suggesting that qualitative sex differences might be expected in the latter domains.

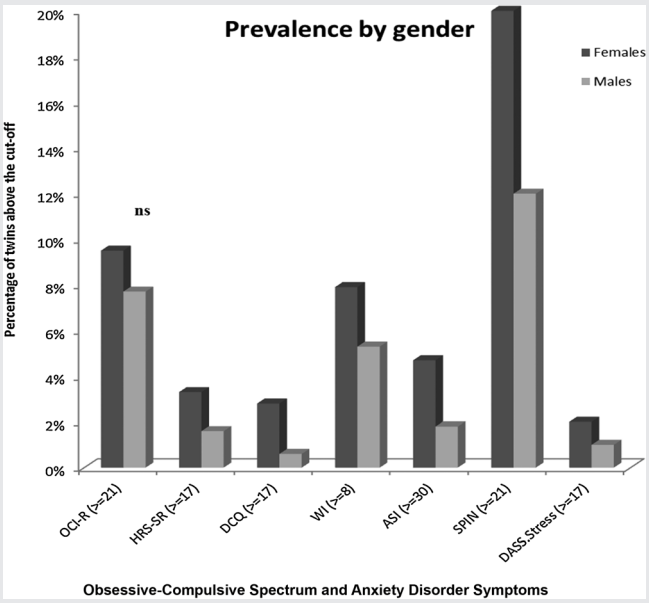

FIG. 2. Percentage of problematic symptoms for male and female based on empirically defined cut-off scores on each scale. OCI-R, Obsessive-Compulsive Inventory–Revised; HRS-SR, Hoarding Rating Scale-Self Report; DCQ, Dysmorphic Concern Questionnaire; WI, Whiteley Index; ASI, Anxiety Sensitivity Index; SPIN, Social Phobia Inventory; DASS.Stress, Depression, Anxiety and Stress Scale-Stress Subscale. ns, Non-significant differences between gender.

Estimation of Heritability

The results of our model-fitting analyses are summarized in Tables IV and V. Consistent with the pattern of observed cross-twin—within-trait correlations, additive genetic factors (A) accounted for a moderate proportion of the total variation in liability to each symptom domain. However, we observed no genetic sex differences in OCI-R, hypochondriasis (WI) and generalized anxiety (DASS-Stress) symptoms. In relation to hypochondriasis and generalized anxiety symptoms, the scalar model demonstrated best fit, indicating a significant difference in phenotypic sex variance.

For OC-related symptoms, we found a tendency for hoarding symptoms (HRS-SR) and DCQ to demonstrate genetic sex differences (Table IV). The quantitative model demonstrated best fit with regard to hoarding after removing the influence of shared environment (C), which significantly improved fit ($P = 0.90$) compared to the quantitative ACE model ($P = 0.63$). Specifically, we identified a tendency towards greater heritability of hoarding symptoms in females (38%) versus males (25%). For DCQ, the qualitative AE model demonstrated best-fit compared to the saturated model, after removing the influence of C ($P = 0.12$). Although this result can only be described as a trend level effect, it was more parsimonious than the full ACE qualitative model ($P = 0.06$). Other reduced models testing quantitative sex differences and non-genetic sex differences did not improve the fit of the data. Therefore, in relation to DCQ, potentially distinct genetic influences occur in this domain between males and females (genetic correlation between both sexes; $rG = 3.58^{-13}$).

In relation to the anxiety traits (Table V), evidence for genetic sex differences was identified in relation to panic (ASI) and social phobia (SPIN) symptoms. For panic symptoms, the qualitative AE model demonstrated best fit when compared with the saturated

TABLE III. Cross-Twin—Within-Trait Correlations for Monozygotic and Dizygotic Twins and Stratified By Sex and Zygosity (n = 2,495 Twins)

Cross-twin-within-trait correlations	MZ (95% CI)	DZ (95% CI)	MZM (95% CI)	DZM (95% CI)	MZF (95% CI)	DZF (95% CI)	DZos (95% CI)
OCI-R	0.41 [0.34, 0.48]	0.17 [0.06, 0.26]	0.40 [0.27, 0.51]	0.16 [−0.03, 0.33]	0.42 [0.32, 0.51]	0.23 [0.09, 0.36]	0.06 [−0.12, 0.23]
HRS-RS	0.33 [0.25, 0.41]	0.15 [0.06, 0.24]	0.25 [0.11, 0.37]	0.14 [−0.05, 0.31]	0.39 [0.29, 0.48]	0.19 [0.05, 0.32]	0.10 [−0.07, 0.27]
DCQ	0.43 [0.36, 0.50]	0.10 [0.006, 0.19]	0.44 [0.32, 0.55]	0.07 [−0.11, 0.25]	0.39 [0.29, 0.49]	0.13 [−0.003, 0.26]	0.03 [−0.14, 0.20]
ASI	0.33 [0.25, 0.40]	0.13 [0.04, 0.22]	0.29 [0.15, 0.41]	0.21 [0.03, 0.38]	0.34 [0.24, 0.43]	0.19 [0.05, 0.32]	0.00 [−0.16, 0.16]
SPIN	0.46 [0.39, 0.52]	0.18 [0.09, 0.27]	0.38 [0.25, 0.49]	0.07 [−0.11, 0.25]	0.49 [0.40, 0.56]	0.24 [0.11, 0.36]	0.16 [−0.01, 0.32]
DASS.Stress	0.36 [0.28, 0.43]	0.16 [0.07, 0.25]	0.32 [0.19, 0.44]	0.21 [0.03, 0.38]	0.35 [0.25, 0.45]	0.16 [0.03, 0.29]	0.10 [−0.06, 0.26]
WI	0.34 [0.26, 0.42]	0.17 [0.08, 0.25]	0.31 [0.18, 0.43]	0.12 [−0.06, 0.30]	0.35 [0.25, 0.44]	0.17 [0.04, 0.31]	0.19 [0.02, 0.34]

MZ, monozygotic; DZ, dizygotic; CI, confidence interval; MZM, monozygotic male twins; DZM, dizygotic male twins; MZF, monozygotic female twins; DZF, dizygotic female twins; DZos, dizygotic opposite-sex twins; OCI-R, obsessive-compulsive inventory–revised; HRS-SR, hoarding rating scale-self report; DCQ, dysmorphic concern questionnaire; ASI, anxiety sensitivity index; SPIN, social phobia inventory; DASS.Stress, stress subscale of the depression, anxiety, and stress scale; WI, Whiteley index.

model ($P = 1$). The full ACE quantitative model did not significantly improve fit ($P = 0.13$), while other submodels showed a significant loss of fit: quantitative AE ($P = 0.09$), scalar ($P = 0.08$), and null ($P = 0.01$). We therefore interpret parameters offered by the qualitative AE model indicating a tendency towards distinct genetic influences between males and females. Finally, for social phobia, females (47%) demonstrated a greater heritability of symptoms compared to males (34%) in the form of a significant quantitative sex difference.

DISCUSSION

This study has examined for the first time the prevalence and heritability of both OC-related and anxiety disorder symptoms in the same twin population of male and female twin pairs. Moreover, this population was particularly well balanced in terms of the age, gender, and sociodemographic characteristics of MZ and DZ twins. As a further novelty, no previous study has investigated the existence of potential genetic sex differences—either due to a lack of male twins or small overall sample size—in relation to hoarding, body-dysmorphic and hypochondriasis symptoms. To summarize, our findings endorse existing evidence for moderate rates of heritability across all of the assessed symptom domains. Significant or trend-level genetic sex differences were detected for hoarding, DCQ, panic, and social phobia symptoms.

Prevalence

Almost nine percent of the overall sample reported OCI-R symptoms that were severe enough to cause distress (OCI-R $\geq$ 21). This is consistent with a recent report of experiencing subclinical OCI-R symptoms (8.3%) in the general population [Adam et al., 2012]. Our estimates support the idea that significant OCI-R symptoms are experienced at a much greater rate in the community than is implied by assessment of diagnostic prevalence alone.

With regard to compulsive hoarding symptoms, we have characterized a similar prevalence rate (2.6%) to the only other twin study utilizing the HRS-SR [2.3%; Iervolino et al., 2009]. For DCQ, we observed a similar prevalence (2%) compared to studies based on the full diagnostic assessment of community-based samples ranging from 0.7% to 2.4% [Faravelli et al., 1997; Otto et al., 2001; Koran et al., 2008].

In relation to anxiety symptoms, 3.5% reported panic-related symptoms, which is consistent with other studies of general community samples reporting a prevalence between 2.5% and 3.4% based on the assessment of diagnostic criteria [Wittchen et al., 2008; Mosing et al., 2009]. In our cohort, social phobia symptoms were slightly higher (16.9%) than in previous epidemiological surveys where diagnostic prevalence rates have been estimated between 7% and 13% [Furmark, 2002; Kessler et al., 2005]. However, as previously emphasized, our study provides symptom-level as opposed to diagnostic-level prevalence estimates. In relation to our measure of generalized anxiety, 5% of individuals reported significant and persistent arousal, tension, and irritability with 1.6% reporting extremely severe of these symptoms that would be considered in the range of other population-based estimates of GAD: 1.9% to 5.1% [Wittchen, 2002]. Lastly, the prevalence of hypochondriasis

TABLE IV. Model-Fitting Analyses to Test Sex Differences for Obsessive-Compulsive Spectrum Traits and their Parameter Estimates

	Model fitting results						Parameters of the models (95% CI)		
							A	C	E
Models (S^2 m/S^2 f)	**−2LL**	**df**	**$\Delta\chi^2$ (Δdf)**	**AIC**	***P***	**Model compared with**	**Male/female**	**Male/female**	**Male/female**
OCI-R (Obsessive-Compulsive Inventory-Revised)									
1. Saturated	7,688	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	7,691	2,486	3.54 (2)	2,719	0.17	1	–	–	–
3. Qualitative ACE (rC = FREE)	7,691	2,486	3.78 (2)	2,719	0.15	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	7,691	2,487	0.24 (1)	2,717	0.63	2	–	–	–
5. Quantitative AE (rG = 0.5; rC = 1)	7,698	2,489	6.89 (3)	2,720	0.08	2	–	–	–
6. Scalar (1.3/1.4)	7,694	2,489	2.51 (2)	2,716	0.29	4	–	–	–
7. Null (1.3)	**7,694**	**2,490**	**2.8 (3)**	**2,714**	**0.42**	**4**	**0.39 (0.18–0.45)**	**0.00 (0.00–0.18)**	**0.61 (0.55–0.68)**
HRS-SR (Hoarding Rating Scale–Self Report)									
1. Saturated	4,047	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	4,047	2,486	0.03 (2)	−925	0.99	1	–	–	–
3. Qualitative ACE (rC = FREE)	4,047	2,486	0.07 (2)	−925	0.97	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	4,047	2,487	0.23 (1)	−927	0.63	2	0.07 (0.00–0.23)/0.38 (0.08–0.47)	0.17 (0.05–0.27)/0.00 (0.00–0.25)	0.76 (0.65–0.88)/0.62 (0.53–0.71)
5. Quantitative AE (rG = 0.5; rC = 1)	**4,047**	**2,489**	**0.6 (3)**	**−930**	**0.90**	2	**0.25 (0.13–37)/0.38 (0.29–0.47)**	–/–	**0.75 (0.63–0.87)/0.62 (0.53–0.71)**
6. Scalar (0.3/0.31)	4,050	2,489	2.8 (0)	−928	<0.001	5	–	–	–
7. Null (0.31)	4,050	2,490	3.4 (2)	−929	0.07	5	–	–	–
DCQ (Dysmorphic Concern Questionnaire)									
1. Saturated[a]	1,046	2,477	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	1,063	2,486	16.6 (9)	−3,909	0.06	1	0.42 (0.20–0.52)/0.38 (0.17–0.47)	0.00 (0.00–0.18)/0.00 (0.00–0.17)	0.58 (0.48–0.70)/0.62 (0.53–0.71)
3. Qualitative ACE (rC = FREE)	1,067	2,486	20.8 (9)	−3,905	0.01	1	–	–	–
4. Qualitative AE (rG = FREE)	**1,063**	**2,488**	**16.6(11)**	**−3,913**	**0.12**	**1**	**0.42 (0.30–0.52)/0.38 (0.28–0.47)**	–/–	**0.58 (0.48–0.70)/0.62 (0.53–0.71)**
5. Quantitative ACE (rG = 0.5; rC = 1)	1,066	2,487	3.2 (1)	−3,908	0.07	2	–	–	–
6. Quantitative AE (rG = 0.5; rC = 1)	1,070	2,489	7.06 (1)	−3,908	0.01	4	–	–	–
7. Scalar (0.09/0.10)	1,066	2,489	3.69 (1)	−3,912	0.05	4	–	–	–
8. Null (.09)	1,074	2,490	11.2 (2)	−3,906	<0.001	4	–	–	–
WI (Whiteley Index)									
1.Saturated	4,262	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	4,262	2,486	−0.37 (2)	−710	1	1	–	–	–
3. Qualitative ACE (rC = FREE)	4,262	2,486	−0.37 (2)	−710	1	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	4,262	2,487	0 (1)	−712	1	2	–	–	–
5. Quantitative AE (rG = 0.5; rC = 1)	4,262	2,489	0.05(3)	−716	1	2	–	–	–
6. Scalar (0.31/0.35)	**4,262**	**2,489**	**0.2 (2)**	**−716**	**0.90**	**4**	**0.29 (0.06–0.39)**	**0.03 (0.00–0.22)**	**0.68 (0.61–0.76)**
7. Null (0.33)	4,265	2,490	3.1 (3)	−715	0.38	4	0.30 (0.06–0.39)	0.02 (0.00–0.21)	0.68 (0.61–0.76)

S^2 m, predicted variance in males; S^2 f, predicted variance in females; rG, genetic correlation for opposite-sex DZ twins; rC, environmental correlation for opposite-sex twins; −2LL, minus twice the log-likelihood; df, degrees of freedom; $\Delta\chi^2$, difference in goodness-of-fit statistic between the submodel and the specified "model compared with"; Δdf, change in degrees of freedom between the submodel and the specified model; AIC, Akaike information criterion [$\chi^2 - 2(df)$]; *P*, probability; A, additive genetic effects; C, shared environmental effects; E, non-shared environmental effects; CI, confidence Interval.

The best fitting models based in AIC are represented in bold text.

[a]Saturated with equal means across zygosity. The rest of the scales are compared with a Saturated with equal means and variance across zygosity.

TABLE V. Model-Fitting Analyses to Test Sex Differences for Anxiety Traits and their Parameter Estimates

	Model fitting results						Parameters of the models (95% CI)		
							A	C	E
Models (S^2 m/S^2 f)	**−2LL**	**df**	**$\Delta\chi^2$ (Δdf)**	**AIC**	***P***	**Model compared with**	**Male/female**	**Male/female**	**Male/female**
ASI (Anxiety Sensitivity Index)									
1.Saturated	7,886	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	7,885	2,486	−0.88 (2)	2,913	1	1	0.27 (0.05–0.41)/0.29 (0.00–0.42)	0.03 (0.00–0.20)/0.04 (0.00–0.31)	0.70 (0.59–0.82)/0.67 (0.58–0.77)
3. Qualitative ACE (rC = FREE)	7,884	2,486	−0.15 (2)	2,912	1	1	–	–	–
4. Qualitative AE (rG = FREE)	**7,885**	**2,488**	**−0.7 (4)**	**2,909**	**1**	**1**	**0.30 (0.18–0.41)/0.34 (0.24–0.42)**	–/–	**0.70 (0.59–0.82)/0.66 (0.58–0.76)**
5. Quantitative ACE (rG = 0.5; rC = 1)	7,887	2,487	2.25 (1)	2,913	0.13	2	0.29 (0.07–0.40)/0.17 (0.00–0.40)	0.00 (0.00–0.16)/0.14 (0.00–0.34)	0.71 (0.60–0.83)/0.69 (0.59–0.80)
6. Quantitative AE (rG = 0.5; rC = 1)	7,888	2,489	2.85 (1)	2,910	0.09	4	0.28 (0.16–0.40)/0.33 (0.23–0.42)	–/–	0.72 (0.60–0.84)/0.67 (0.58–0.76)
7. Scalar (1.3/1.5)	7,888	2,489	3.05 (1)	2,910	0.08	4	–	–	–
8. Null (1.4)	7,894	2,490	9.44 (2)	2,915	0.01	4	–	–	–
SPIN (Social Phobia Inventory)									
1.Saturated	8,803	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	8,804	2,486	1.09 (2)	3,832	0.60	1	–	–	–
3. Qualitative ACE (rC = FREE)	8,804	2,486	1.30 (2)	3,833	0.52	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	8804.4	2,487	0.20 (1)	3,831	0.65	2	0.35 (0.15–0.45)/0.44 (0.17–0.54)	0.00 (0.00–0.14)/0.04 (0.00–0.27)	0.65 (0.55–0.77)/0.53 0.45–0.62)
5. Quantitative AE (rG = 0.5; rC = 1)	**8804.5**	**2,489**	**0.28 (3)**	**3,826**	**0.96**	**2**	**0.34 (0.23–0.45)/0.47 (0.39–0.55)**	–/–	**0.66 (0.55–0.77)/0.53 (0.45–0.61)**
6. Scalar (2.06/2.11)	8,808	2,489	3.63 (0)	3,830	<0.001	5	–	–	–
7. Null (2.09)	8,808	2,490	3.85 (1)	3,828	0.05	5	–	–	–
DASS.Stress (Depression, Anxiety, and Stress Scale—Stress Subscale)									
1.Saturated	6,615	2,484	–	–	–	–	–	–	–
2. Qualitative ACE (rG = FREE)	6,614	2,486	−0.65 (2)	1,642	1	1	–	–	–
3. Qualitative ACE (rC = FREE)	6,614	2,486	−0.34 (2)	1,642	1	1	–	–	–
4. Quantitative ACE (rG = 0.5; rC = 1)	6,614	2,487	0.31 (1)	1,640	0.60	2	–	–	–
5. Quantitative AE (rG = 0.5; rC = 1)	6614.5	2,489	0.54 (3)	1636.5	0.92	2	–	–	–
6. Scalar (0.80/0.89)	**6614.5**	**2,489**	**−0.07 (0)**	**1636.5**	**1**	**5**	**0.32 (0.09–0.40)**	**0.006 (0.00–0.20)**	**0.67 (0.60–0.75)**
7. Null (0.85)	6,618	2,490	3.73 (1)	1,638	0.05	5	–	–	–

S^2 m, predicted variance in males; S^2 f, predicted variance in females; rG, genetic correlation for opposite-sex DZ twins; rC, environmental correlation for opposite-sex twins; −2LL, minus twice the log-likelihood; df, degrees of freedom; $\Delta\chi^2$, difference in goodness-of-fit statistic between the submodel and the specified "model compared with"; Δdf, change in degrees of freedom between the submodel and the specified model; AIC, Akaike information criterion [$\chi^2 - 2$(df)]; *P*, probability; A, additive genetic effects; C, shared environmental effects; E, non-shared environmental effects; CI, confidence Interval.
The best fitting models based in AIC are represented in bold text.

symptoms (6.8%) was similar to that reported in a recent survey of health anxiety in Australia (6%) [Sunderland et al., 2013].

Significantly higher prevalence rates in females compared to males were observed across all measures with the exception of OCI-R symptoms, which taken together is generally consistent with prior studies in community samples [Faravelli et al., 1997; Rief et al., 2006; Koran et al., 2008; Adam et al., 2012; Kessler et al., 2012]. The highest prevalence rate in females was in relation to social phobia, which accords well with previous estimates [Magee et al., 1996; Lampe et al., 2003]. More controversy surrounds hypochondriasis and compulsive hoarding. Epidemiological studies of hypochondriasis are in fact very rare. Two initial studies found no gender differences in hypochondriasis [Gureje et al., 1997; Escobar et al., 1998]. However, a representative study [Rief et al., 2001] noted significantly higher scores in women, but with a small effect size. Least consistent have been gender-based prevalence estimates in compulsive hoarding [Frost et al., 2012]. Two epidemiological studies have reported compulsive hoarding to be more prevalent in males than females [Samuels et al., 2008; Iervolino et al., 2009], although one study [Samuels et al., 2008] did not use a standardized questionnaire to assess hoarding. In the same direction as our results, studies of clinical samples indicate a higher prevalence of compulsive hoarding disorder in females [Steketee and Frost, 2003; Pertusa et al., 2008; Mataix-Cols et al., 2010].

Heritability

Our findings indicate familial aggregation in all symptoms assessed as observed in the pattern of cross-twin—within-trait correlations. The heritability analyses suggest that this familiarity is primarily attributable to genetic factors and not to the shared environment. The results of the twin analyses indicate that genetic factors account for between 30% (i.e., hypochondriasis) and 47% (i.e., social phobia in females), which is consistent with moderate genetic factors contributing to the aetiology of the symptom domains assessed.

The heritability rates for OCI-R symptoms and hypochondriasis appear to be in line with past studies [van Grootheest et al., 2005; Taylor et al., 2006]. Similarly, a recent study of OCI-R symptoms did not report evidence of genetic sex differences [Mataix-Cols et al., 2013]. Ours is the first twin study to suggest no prominent genetic sex differences in relation to hypochondriasis symptoms in adults, extending the only other twin study of hypochondriasis symptoms [Taylor et al., 2006]. For hoarding symptoms we observed a lower heritability rate (38%, female; 25%, males) when compared to the recent study by Iervolino et al. (49% female only). These rates may be explained by the prominent age differences between studies, with the latter study including female twins who were on average two decades older than our current sample, inclusive of elderly twins. When comparing genders, our results indicate a higher heritability of hoarding symptoms in females. This result contrasts with the only other twin study of hoarding symptoms to formally test for genetic sex differences [Ivanov et al., 2013]. In adolescents, Ivanov et al. [2013] reported quantitative sex differences, with genetic influences in boys accounting for considerably more phenotypic variance than in girls (32% vs. 2%). These authors invoked the notion of dynamic developmental genetic and environmental influences operating between adolescence and adulthood in order to explain the low heritability rate observed in young female twins. By adulthood, our results suggest a reversed pattern of heritability, although the actual rates being more similar between females and males. Clearly, further studies are needed to understand how gender impacts on the etiology of hoarding taking into account developmental trajectories.

In relation to DCQ, we observed a similar rate of heritability (42% vs. 44%) to the recent study by Monzani et al. [2012a]. Our results extend their work by indicating a trend towards qualitative sex differences, meaning that different biological risk factors may underlie the manifestation of these symptoms in females and males. The DCQ, as used in our current study, may be considered to represent quite a broad phenotype that captures body image concerns also common to eating disorders, which are more prevalent in females [Smink et al., 2012]. Interestingly, recent studies examining putative biological risk factors for such disorders in twin populations have provided some evidence for distinct developmentally mediated sex liability mechanisms, including levels of prenatal testosterone exposure [Culbert et al., 2008]. It remains untested whether such mechanisms may contribute to sex differences in risk towards body DCQ in addition to eating disorders.

In relation to anxiety symptoms, we found a similar heritability for social phobia symptoms in males compared to a recent study based on the full assessment of DSM criteria (34% vs. 39%) [Mosing et al., 2009]. When compared to studies that have assessed social phobia symptoms using the fear of negative evaluation scale, our heritability estimate is closest with regard to female twins (47% vs. 48%) [Stein et al., 2002]. While some studies have reported no heritable sex differences in fear and phobia (including social phobia) [Hettema et al., 2005; Middeldorp et al., 2005], another study reported that social phobia in males was explained by genetic risk factors and in females by familial-environmental factors [Kendler et al., 2002]. However, two additional twin studies performed separately in males and females reported lower heritability in males (20%) [Kendler et al., 2001] than females (30%) [Kendler et al., 1992a]. This latter pattern is more in agreement with our finding of a quantitative sex difference and with a recent meta-analysis in separation anxiety disorder (associated with social phobia in adulthood [Hofmann et al., 2004]), where genetic risk was reported to be double in females (52%) compared to males (26%) [Scaini et al., 2012].

For panic symptoms, we estimated a similar heritability (30–34%) compared to previous panic disorder-level estimates [33% in Tambs et al., 2009; 38% in Mosing et al., 2009], but a lower rate as compared to a former population-based study of the ASI (45%, 95% CI = 0.33–0.59) [Stein et al., 1999]. This latter difference could be due to the reduced number of male twin pairs in the Stein et al. study, potentially leading to an overestimation of heritability in their case [Van Dam et al., 2009]. Regarding gender, we found a tendency for qualitative differences, which means that a partially different set of genes might mediate the risk towards panic-related symptoms in men and women. Biological sex differences have been recently suggested in experimental studies of physical panic attack symptoms associated with a CO_2 challenge [Nillni et al., 2012]. In this study, sex differences were related to the experience of the physical symptoms of panic rather than its cognitive correlates. Our

results may also be in line with animal studies reporting a role for sex-specific hormones (i.e., progesterone) in the manifestation of anxiety and panic [Smith et al., 2006]. Along these lines, premenstrual distress has been shown to predict higher levels of panic symptoms following a CO_2 challenge [Nillni et al., 2010].

Lastly, our estimated heritability of 32% for the Stress subscale of DASS-21—our proxy measure of GAD symptoms—accords with other studies reporting the heritability of GAD [28–32.5%; Kendler et al., 2007] and when we compare to a more broadly trait of neuroticism [30–50%; Calboli et al., 2010]. A lack of evidence for genetic sex differences has also been previously noted in GAD [Hettema et al., 2005].

Limitations

Although the "dimensional liability" approach adopted here and in other twin studies is a valid and widely employed method in behavioural genetics [Jonnal et al., 2000; Hettema et al., 2001; van Grootheest et al., 2005], it will nonetheless be important to replicate these findings in clinical populations. Secondly, the use of initial screening questions is likely to have precluded our ability to attain a sufficient sample to estimate heritability for skin picking and hair pulling symptoms. However, low response rates may have been anticipated for these domains compared to others, particularly in the case of compulsive hair-pulling symptoms. Thirdly, results from Stress subscale of DASS-21 are interpreted as a proxy measure of GAD symptoms but there is reason to believe it may index a broader vulnerability trait to anxiety and depression—the so-called "general neurotic syndrome" [Henry and Crawford, 2005]. Nevertheless, previous twin studies that have assessed the genetic overlap between GAD and major depressive disorder suggest that both disorders share a strong common genetic liability [Kendler et al., 1992b; Kendler et al., 2007]. Indeed, within our sample there was a strong genetic correlation (r_A) between the Stress and Depression subscales of the DASS-21 $r_A = 0.84$.

While it is difficult to definitively exclude potential sampling biases in relation to surveys such as this [i.e., "accidental sampling method"; Powell, 1997], there are reasons to believe our results are generalizable to the population at large. For example, although our estimate of severe OC-symptoms appears high (8.7%), this rate is reduced to 2.7% when taking into account a personal history of OCD. Importantly, both estimates are consistent with a recent report of the 12-month prevalence of anxiety disorders in the Australian population [McEvoy et al., 2011]. Furthermore, as discussed above, other characteristics of this twin population, such as differences in prevalence of symptoms between genders also appears to be consistent with previous literature.

CONCLUSION

This is the first study to have assessed the prevalence and heritability of OC-related and anxiety symptoms together in an adult twin population. Novel findings include the observation of probable genetic sex differences in liability to hoarding and DCQ symptoms, as well as the lack of such differences in hypochondriasis. The trend towards qualitative sex differences in relation to the heritability of panic symptoms has some intuitive appeal with regard to biological-experimental studies of panic.

Multivariate twin studies will now be important for clarifying the extent to which these symptom domains express common or distinct genetic risk factors. Such studies are likely to be valuable in addressing ongoing debate about the optimal diagnostic classification of OCD in relation to anxiety disorders and the contribution of anxiety more broadly to the etiology of OCD.

ACKNOWLEDGMENTS

This research was facilitated through access to the Australian Twin Registry, a national resource supported by an Enabling Grant (ID 628911) from the National Health and Medical Research Council. We extend considerable thanks to staff at the Australian Twin Registry and all participating twins for their valuable contribution to this study. We also thank Dr. Fruhling Rijsdijk for her advice on some of the statistical analyses included herein. This study was funded by an Early Career Researcher Grant from The University of Melbourne to BJH. BJH is supported by a National Health and Medical Research Council of Australia (NHMRC) Clinical Career Development Fellowship (I.D. 628509). C.L-S. is supported by the Spanish Ministry of Education, Culture and Sport (FPU12/01636). C.S-M. is funded by a 'Miguel Servet' contract from the Carlos III Health Institute (CP10/00604). Prof. C.P was supported by a NHMRC Senior Principal Research Fellowship (ID: 628386) and NARSAD Distinguished Investigator Award. Prof. M.Y was supported by a NHMRC Senior Research Fellowship (ID: 1021973).

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