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Obsessive–compulsive disorder, tics and anxiety in 6-year-old twins

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ABSTRACT

Background. Previous reports of genetic influences on obsessive–compulsive disorder (OCD) symptoms have suggested moderate heritability. Family history studies of co-morbidity have found familial aggregation with tics, especially for early-onset OCD, and familial aggregation with anxiety disorders.

Method. Heritability of OCD and familial aggregation of OCD, tics and anxiety disorders were investigated in a community sample of 6-year-old twins using a two-phase design in which 4662 twin pairs were sampled and 854 pairs were assessed in the second phase by maternal-informant diagnostic interview using DSM-IV criteria.

Results. In the multivariate model combined additive genetic and common environmental effects were estimated as 47% for sub-threshold OCD, and the model was unable to distinguish these sources of familial aggregation. There were strong familial aggregations between sub-threshold OCD and tics and between sub-threshold OCD and other anxiety disorders (80% and 97% respectively), although again specific sources could not be distinguished.

Conclusions. The findings are consistent with the hypothesis of a tic-related early-onset OCD phenotype, but also with the hypothesis of an anxiety-related early-onset OCD phenotype.

INTRODUCTION

The main aim of the present study was to investigate genetic and environmental influences on paediatric obsessive–compulsive disorder (OCD) and on its associations with tics and with anxiety disorders. Key points in the literature – recently reviewed in Hettema *et al.* (2001), Shih *et al.* (2004) and van Grootheest *et al.* (2005) – include the following.

Large-scale twin studies of OCD symptoms are rare, and there have been no studies of a diagnostically defined phenotype. Clifford *et al.* (1984) gave the Leyton Obsessional Inventory to 419 pairs of non-clinic referred twins, estimating heritability for its trait and symptom scales as 47% and 44% respectively. More recently Jonnal and colleagues (2000) reported a sample of 527 adult female twin pairs who completed 20 items from the Padua Inventory of obsessive compulsive symptoms and estimated heritability of the two main factors, corresponding roughly to obsessions and compulsions; the best-fit model suggested additive genetic heritabilities of 33% and 26% respectively. Hudziak and colleagues (2004) assessed large samples of twins aged 7, 10 and 12 years in cohorts from Holland and the USA using an 8-item Obsessive–Compulsive Scale contained in the Child Behavior Checklist. Best-fitting models indicated significant additive genetic influences in the range 45–58%, with significant shared environmental influence detected only in the Dutch 12-year-old cohort (16%). Genetic influences on OCD have been studied mainly using the family history method, sensitive

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to familial aggregation, but not directly to the distinction between genetic and shared environmental influences. Family studies in the 1980s/1990s consistently found that relatives of OCD probands had raised rates of OCD or sub-threshold OCD compared to non-clinic controls ranging between 4% and 35%, this large range partly reflecting variable criteria for 'sub-threshold' OCD (Lenane *et al.* 1990; Riddle *et al.* 1990; Bellodi *et al.* 1992; Leonard *et al.* 1992; Thomsen, 1995). More recent family history studies have suggested that familial aggregation of OCD may apply only to early-onset OCD (<18 years) (Nestadt *et al.* 2000; Carter *et al.* 2004), and even then not in all cases (Chabane *et al.* 2005).

Much of the family history research on OCD has focused on co-morbidity and its implications for genetic association. Following the finding that paediatric OCD is often associated with tics, a seminal family history study by Pauls and colleagues (1986) used a novel method depending on proband co-morbidity. They found that probands with tic disorder without OCD were as likely to have relatives with OCD as probands with tic disorder but with OCD, from which it was inferred that OCD is an alternate expression of the genes for tic disorder. A further study by the Yale group (Pauls *et al.* 1995) began with OCD probands and examined rates of tics and OCD and sub-threshold OCD in first-degree relatives compared with non-clinical controls, finding higher rates of tics among relatives of OCD probands than controls (4·6% *v.* 1·0%). The study also found that relatives of early-onset OCD cases (<18 years) were more likely to have both OCD and tics, with greatest risk in case of onset between ages 5 and 9 years. This suggests that childhood onset OCD may be the more heritable form (associated with tics). Finally, the Yale group study found that rates of tics were higher in relatives of OCD probands with a family history of OCD compared with those without family history, consistent with the hypothesis that tic-related OCD is a distinctive familial subtype. Subsequent family history studies have supported the hypothesis that tic disorders constitute an alternate expression of the familial OCD phenotype (Grados *et al.* 2001; Hanna *et al.* 2005). Much of this work has been with clinic samples, which may have greater co-morbidity. Two studies of early-onset OCD in community cohorts have failed to find association between tics and the disorder (Flament *et al.* 1988; Douglass *et al.* 1995).

Family history methodology has also been used to examine the association between OCD and other anxiety disorders. Family history studies of OCD that included an anxious non-OCD control group did not find raised rates of obsessive–compulsive symptoms in first-degree relatives compared with those controls (Clark & Bolton, 1985; Last *et al.* 1991). A family study by Black and colleagues (1992) found that the rates of sub-threshold OCD and anxiety disorder were higher among the relatives of adult probands with OCD compared with relatives of psychiatrically normal controls, suggesting that anxiety disorder diathesis is transmitted in families with OCD, consistent with the classification of OCD as an anxiety disorder. Subsequent analysis using the methodology of Pauls *et al.* (1986) described above compared psychiatric disorders in the relatives of probands with OCD and non-clinic controls, finding a raised rate of generalized anxiety disorder (GAD) in OCD relatives of OCD probands, including those without co-morbid GAD, suggesting that GAD may represent an alternative expression of the genetic factor(s) contributing to OCD (Black *et al.* 1995). Recent study using similar family history methodology also with adult samples have found familial aggregation of OCD and GAD (Nestadt *et al.* 2001), and of OCD and anxiety disorders, more strongly for OCD with early onset (<10 years) (Carter *et al.* 2004). To date there have been no reported family history studies of OCD co-morbidity with anxiety disorders for child probands, and no reports of OCD co-morbidity with anxiety disorders or tics using twin methodology.

The present twin study was designed to address the following sets of questions. First, is there familial aggregation of early-onset OCD using well-defined criteria for sub-threshold caseness in a population sample, and if so, to what extent is this attributable to genetic influence? Second, is early-onset OCD associated with tics in a community sample, and is there familial aggregation of these two conditions? Is there also familial aggregation of OCD and anxiety disorders? Third, to what extent is familial aggregation of these three conditions attributable to genetic influence? The study

design and sample also allowed us to obtain an estimate of heritability of tics in a community sample.

METHOD

Design: two-phase stratified sampling

The present study is part of the Institute of Psychiatry's Genetic and Environmental Effects on Emotion Study (GEMS), and the basic methodology and procedure have been reported elsewhere (Bolton *et al*. 2006). In summary, a standard two-phase stratified sampling design was used, the first phase comprising 4662 twin pairs in the Twins Early Development Study (TEDS; Trouton *et al*. 2002). Of the 4662 twin pairs in the Phase 1 sample, 754 were monozygotic male (MZM), 783 dizygotic male (DZM), 845 monozygotic female (MZF), 768 dizygotic female (DZF), and 1512 were dizygotic opposite-sex (DZO) pairs. The Phase 1 sample were screened at age 4 using a maternal-informant composite questionnaire on anxiety-related behaviours and tics, and a high-risk sample defined by scores on the screening instrument were selected, along with a control group, for detailed assessment in Phase 2 at age 6 years, in the first half of their seventh year. The selection criterion identified 1833 screen-positive twin pairs, that is, twin pairs with at least one of the twins screen-positive, with the remaining 2829 pairs being screen-negative, that is, pairs with neither child screen-positive. Of the 1833 screen-positive twin pairs 1296 were available for the present study, and of the 2829 screen-negative pairs 2318 were available, the others being unavailable because of participation in other studies. Thus, for assessment in Phase 2, all available 1296 screen-positive twin pairs were selected for study, together with a control group of 192 screen-negative twin pairs selected randomly from the 2318 available, making a total of 1488 twin pairs (2976 children).

In two-phase sampling designs Phase 2 data-points are adjusted by selection probability strata weights, computed as the inverse of the proportion of the number of Phase 2 observations in a given stratum (defined by scores on the Phase 1 screen) to the number in that stratum in the Phase 1 sample. The standard principle for epidemiological surveys by which selection probability strata weights are attached to the data-points of individuals (observed in Phase 2) has to be qualified in the case of twin population samples. Because in twin analyses pairs and not individuals are the units of study, weights are assigned to pairs. In the case of a binary classification, as used in the present study, the principle is that a twin pair is assigned a screen-positive weight in case either co-twin, but not necessarily both, is screen-positive, and is assigned a screen-negative weight in case both co-twins are screen-negative. The same selection probability weights are used for estimating prevalence rates.

Ethical approval for the study was given by the Research Ethics Committee of the Institute of Psychiatry and South London and Maudsley NHS Trust, and written informed consent was obtained from the mothers participating in the study.

Phase 2 observed sample

The sample observed in Phase 2 consisted of 1708 children, aged between 6 and $6\frac{1}{2}$ years, comprising 854 twin pairs, 253 MZ, and 601 DZ. Response rate was 57% ($n=854/1488$ twin pairs). Main reasons for non-participation in Phase 2 were, as percentages of the whole selected sample ($n=1488$ families) and in order of size of the groups, as follows: failure to return written consent forms or failure to arrange the interview before the time window for the assessment elapsed (i.e. before twins exceeded $6\frac{1}{2}$ years) (20%), untraceable (12%), 'too busy to participate' (5%), with the remaining 5% due to miscellaneous other reasons.

Assessments in Phase 2

In Phase 2 diagnostic status according to DSM-IV was assessed by telephone interview with the mothers using the parental version of the Anxiety Disorders Interview Schedule for Children and Parents (ADIS-C/P; Silverman & Nelles, 1998), amended to assess lifetime diagnoses. In the present study a distinction was made between 'symptom syndrome' and 'diagnosis'. A child was assigned a 'symptom syndrome' where they met the full DSM-IV symptom criteria for a disorder *regardless of degree of impairment*, defined according to ADIS-C/P rules. Diagnoses were only assigned where the child met both the symptom

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syndrome criterion and associated impairment criterion. Full details of amendment and use of the ADIS-C/P are given in our previous report (Bolton *et al*. 2006).

A section on tics was appended to the diagnostic interview, obtained from the Yale Child Study Center (J. Leckman, personal communication, 1999). This comprised a paragraph explaining to the interviewee what tics are, and a subsequent explanatory paragraphs on motor tics, followed by the question: 'Has your child ever had (or does he/she now have) facial tics, jerks of other parts of the body, or any unusual movements or habits?' If the answer to this question was 'yes', information was sought on the nature of the tic, on frequency, including whether nearly every day, onset, including whether at least a month ago, or at least a year ago, duration, including whether for at least 4 months or at least a year, and whether there has ever been a tic-free period of at least three consecutive months. There follows a subsection on vocal tics, prefaced by an explanatory paragraph, then the question: 'Have you ever found (or do you find now) your child making involuntary noises other than normal talking, like grunts, throat clearing, or saying words or part of words?' If the answer to this question was 'yes', information was sought as above on the nature, frequency, and duration of tics and of tic-free periods. This information is sufficient to establish according to DSM-IV criteria presence of absence of transient tic disorder, chronic motor or vocal tic disorder and Tourette's disorder.

Phenotypes examined in the present study

Symptom syndrome is a plausible phenotype in genetic studies, and has the advantage that it is more common than diagnosis, providing greater statistical power to detect effects. To maximize numbers, lifetime symptom syndrome phenotypes were selected for consideration in the case of the rarer conditions, OCD and tics. In the case of OCD, again to maximize numbers, a phenotype sub-threshold for symptom syndrome (and diagnosis) was also considered, defined straightforwardly using ADIS/C-P rules, as follows: (*a*) positive response to screen for obsessions or for compulsions, and (*b*) positive response to 'persistence'; but *without requiring* significant distress at the symptom level or resistance (trying to stop). In the case of tics, we selected as the tic disorder phenotype transient plus chronic tic disorder lifetime symptom syndrome (that is, requiring motor or phonic tics of at least 4 weeks duration). A general category of any anxiety disorder other than OCD was defined, comprising separation anxiety disorder, social phobia, specific phobia, and GAD, post-traumatic stress disorder and panic disorder. This general category was much more common in the sample than tics or OCD, and to reduce this effect any anxiety disorder lifetime diagnosis (rather than syndrome) was selected for consideration. Thus the following three conditions were considered in testing hypotheses in the present study: OCD lifetime sub-threshold syndrome, tic disorder lifetime syndrome, and any anxiety disorder (other than OCD) lifetime diagnosis. Kappa coefficients for assessment of these three conditions were obtained using the method described in our previous report (Bolton *et al*. 2006) and were as follows: 0·80 for OCD lifetime sub-threshold syndrome, 0·80 tic disorder lifetime syndrome, and 0·88 for any anxiety disorder (other than OCD) lifetime diagnosis.

For these three conditions weighted prevalence rates in the whole sample ($n=9324$ individuals), with 95% confidence intervals (CIs), and with raw (unweighted) numbers in the Phase 2 sample ($n=1708$ individuals) in square brackets, were as follows: for OCD lifetime sub-threshold syndrome (6·1%, 95% CI 4·2–8·5 [136]); for tic disorder lifetime syndrome (6·0%, 95% CI 4·2–8·4 [124]); and for any anxiety disorder (other than OCD) lifetime diagnosis (19·1%, 95% CI 16·1–22·4 [456]). For comparison purposes, the rate for OCD lifetime syndrome was 2·5% (95% CI 1·4–4·3 [57]), indicating that the broadening of the phenotype to include sub-syndromal cases approximately doubled the prevalence rate.

Statistical methods

All analyses incorporated selection probability weights as defined above to account for selection of the sample assessed in Phase 2. Prevalence rates were computed on weighted data using STATA statistical software for survey data (Stata Corporation, 2004), which also permitted control for the effects of 'clustering' of conditions in the twin pairs. To investigate the

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hypotheses of the study, multivariate genetic analyses were applied to three variables: OCD lifetime sub-threshold syndrome, tic disorder lifetime syndrome, and any anxiety disorder (other than OCD) lifetime diagnosis. These conditions are defined above and for brevity are shortened, using italics, to *OCD*, *Tics*, and *Anxiety disorder*. Analytical methodology is as follows:

Liability-threshold model fitting

Since all variables were dichotomous ('no' = 0, 'yes' = 1), tetrachoric correlations and parameters of the genetic models were estimated using liability-threshold models fitted in the programme Mx (Neale, 1999). The assumption is that each symptom dimension has an underlying normal distribution of liability with a discrete threshold (above which a child is assumed to show the condition of relevance) and that the joint liabilities (e.g. twin 1 and twin 2 scores) follow a bivariate normal distribution where both traits have a mean of 0 and standard deviation 1. The correlation between the liabilities and the thresholds are estimated from the relative proportions in each category (i.e. number of pairs where both twins score 'yes', or 'no', or are discordant). For the simultaneous analyses of three or more dichotomous variables Mx provides raw ordinal maximum-likelihood estimation. Essentially, the model predicts proportions of twin pairs that should exist for the various possible patterns of responses from two twins, assuming a multivariate normal distribution. These expected proportions are then evaluated against the observed cell proportions to derive a maximum-likelihood correlation matrix for both MZ and DZ twin pairs.

Tetrachoric correlations between OCD, Tics *and* Anxiety disorder

The MZ and DZ correlations between the six dichotomous traits (i.e. *OCD*, *Tics* and *Anxiety disorder* for twin 1 and twin 2) were estimated in a constrained model that produced a reduced number of correlations to simplify interpretation: three within-twin cross-trait correlations (equal across MZ and DZ pairs); three cross-twin within-trait correlations (MZ and DZ pairs, separately); and three cross-twin cross-trait correlations (MZ and DZ pairs, separately). These correlations will indicate if there are common aetiological influences on the three liabilities and to what extent these influences are due to overlapping genetic, shared-environmental and non-shared-environmental effects. These sources of covariance are formally tested in the genetic model (see below).

Genetic model fitting

Genetic model fitting of twin data estimates the contribution of genetic and environmental influences to individual differences in a trait. Three latent components are inferred from the data: additive genetic influence (A), shared or common environment (C), and non-shared environment (E). Identical (MZ) share all their genes whilst non-identical (DZ) twins share only 50% of their genes. Assuming that MZ and DZ twins are equally similar in terms of their environment, then any excess of similarity between MZ twins over DZ twins is assumed to be due to the greater genetic sharing for MZ twins, thus giving estimates of genetic effects. Resemblance between MZ twins not due to genetic effects is assumed to be due to the shared environment (C), and differences between MZ twins are attributable to differing environmental impacts on the individuals and thus permit estimate of E. The relative magnitude and importance of these latent factors can be inferred by fitting the raw ordinal data (with observed correlational patterns) to the predicted correlations according to the hypothesized model (ACE, AE, CE or E). Full details of this method are given elsewhere (Neale & Cardon, 1992; Plomin *et al*. 2001).

In addition, when multiple liabilities are measured, their associations (implying common aetiological influences) can be partitioned into genetic, shared-environmental and non-shared-environmental correlations. The power to distinguish between these different sources of co-occurrence is derived from the MZ/DZ ratio of these correlations: a 2:1 ratio is indicative of additive genetic effects, whereas a 1:1 ratio suggests influences of common environment in inducing a correlation between two variables. Non-significant cross-trait cross-member correlations imply that the common aetiological influences are due to individual specific environment (E), not familial effects.

A full Cholesky ACE decomposition was fitted to the data, and nested sub-models were

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Table 1. *Tetrachoric correlations within- and cross-twins, and within- and cross-traits (with 95% CI) for* OCD, Tics *and* Anxiety disorder

	Within-twin cross-trait	Cross-twin within-trait		Cross-twin cross-trait		
	Whole sample	MZ pairs	DZ pairs	Whole sample	MZ pairs	DZ pairs
OCD	—	0·57 (0·24–0·80)	0·22 (−0·02–0·43)	—	—	—
Tics	—	0·64 (0·35–0·82)	0·33 (0·09–0·54)	—	—	—
Anxiety disorder	—	0·54 (0·34–0·69)	0·39 (0·27–0·51)	—	—	—
OCD–Tics	0·32 (0·17–0·45)	—	—	0·25 (−0·06–0·42)	0·19 (−0·06–0·42)	0·28 (0·10–0·43)
OCD–Anxiety disorder	0·25 (0·14–0·36)	—	—	0·23 (0·12–0·34)	0·25 (0·06–0·43)	0·22 (0·09–0·34)
Tic–Anxiety disorder	0·14 (0·02–0·26)	—	—	0·16 (0·07–0·28)	0·18 (−0·02–0·36)	0·16 (0·02–0·29)

The within-twin cross-trait correlations were constrained cross twins such that, e.g. $OCD_{twin1} - Tics_{twin1} = OCD_{twin2} - Tics_{twin2}$. The cross-twin cross-trait correlations are constrained such that, e.g. $OCD_{twin1} - Tics_{twin2} = OCD_{twin2} - Tics_{twin1}$. Confidence intervals including zero indicate non-significance. Thresholds for MZ pairs were: 1·50, 1·47, 0·64, and for DZ pairs: 1·37, 1·47, 0·64.

Table 2. *Multivariate genetic model-fitting results (raw ordinal analyses with weights)*

Model	χ^2	df	*p* value	AIC	$\Delta\chi^2$	Δdf	*p* value
(1) ACE	18·5	21	0·62	−23·5	—	—	
(2) CE	23·8	27	0·64	−30·2	5·35	6	0·49
(3) AE	24·2	27	0·62	−29·8	5·8	6	0·45
(4) E	496	33	<0·001*	423	477	12	<0·001*
ACE							
(5) No $r_g + r_c$ *OCD–Tics*	28·9	23	0·18	−17·1	10·4	2	0·005
(6) No $r_g + r_c$ *OCD–Anxiety disorder*	33·7	23	0·07	−12·3	15·2	2	0·001
(7) No $r_g + r_c$ *Tics–Anxiety disorder*	18·5	23	0·73	−27·5	0	2	1

Models 5, 6 and 7 test the significance of a familial correlation between the traits. r_g and r_c are the genetic and shared-environmental correlation, respectively and are reported in Table 4. $\Delta\chi^2$ is derived by comparing sub-models to the full ACE model. The critical χ^2 value (at the 0·05 level) for 1 df is 3·84.

AIC, Akaike's Information Criterion ($\chi^2 - 2$ df), so that higher negative values indicate a better fit.

* Significant decline in fit.

evaluated. Since analyses on raw data produces a log-likelihood of the data, to obtain an overall measure of fit (χ^2), we need to compute the difference in likelihoods between each genetic model and a perfect fitting (saturated) model in which the maximum number of parameters is estimated to describe the correlational structure between all variables. We have only reported the χ^2 indices here (Table 2). The fit of all models were assessed by the χ^2 statistic and degrees of freedom of the model; a non-significant χ^2 indicates a good-fitting model. The fit of nested sub-models (e.g. AE or CE) compared with the full model were evaluated by changes in χ^2 relative to the associated change in degrees of freedom, and comparison of sub-models with the same number of parameters used Akaike's Information Criterion (AIC, $\chi^2 - 2$ df), by which higher negative values indicate a better fit (Neale & Cardon, 1992). Information about the precision of parameter estimates was obtained by likelihood-based CIs (Neale & Miller, 1997).

RESULTS

The first set of questions the present study aimed to address is whether individual differences in paediatric OCD, tics and anxiety disorder show familial aggregation effects (due to either genetic or shared environmental influences). Relevant results here, as for other questions addressed, are all from the multivariate modelling. Table 1 shows tetrachoric correlations within and cross twins, and within

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Table 3. *Standardized estimates (with 95% CI) based on the full ACE model*

	A			C			E		
	OCD	*Tics*	*Anxiety disorder*	*OCD*	*Tics*	*Anxiety disorder*	*OCD*	*Tics*	*Anxiety disorder*
OCD	0·29 (0·00–0·68)			0·18 (0·00–0·48)			0·53 (0·28–0·80)		
Tics	0·12 (0·00–0·40) [36%]	0·50 (0·00–0·78)		0·14 (0·00–0·35) [44%]	0·11 (0·00–0·55)		0·06 (0·00–0·25) [19%]	0·39 (0·19–0·67)	
Anxiety disorder	0·07 (0·00–0·31) [28%]	0·03 (0·00–0·20) [20%]	0·25 (0·00–0·63)	0·17 (0·00–0·31) [69%]	0·13 (0·00–0·24) [76%]	0·27 (0·00–0·51)	0·01 (0·00–0·15) [3%]	0·01 (0·00–0·10) [4%]	0·48 (0·32–0·66)

On the diagonals of the A column, are the heritabilities of the traits and on the diagonals of the C and E columns the standardized shared-environmental variance (c^2), and non-shared environmental variance (e^2), respectively. On the off-diagonals are the phenotypic correlations due to A, C, E (with 95% CI), with the proportions given in square brackets. These values are a function of both the standardized estimates on the diagonals and the A, C and E correlations given in Table 4, and add up to the phenotypic correlation (last column Table 4).

and cross traits, with 95% CIs, for the three phenotypes *OCD*, *Tics* and *Anxiety disorder*.

The higher MZ compared to DZ cross-twin within-trait correlations (second column in Table 1), indicate genetic influences, especially for *OCD* and *Tics*. Results of the formal testing of the significance of genetic and environmental effects are presented in Table 2.

Dropping either all genetic parameters (for *OCD*, *Tics* and *Anxiety disorder*) or all shared-environmental parameters (models 2 and 3) did not result in a significant decline in fit [$\Delta\chi^2$ (6 df) = 5·35, $p = 0{\cdot}49$, and 5·8, $p = 0{\cdot}45$ respectively]. However, dropping A and C at the same time showed a highly significant deterioration in fit [$\Delta\chi^2$ (12 df) = 477, $p < 0{\cdot}001$]. This means that, although there are highly significant familial effects on each of the traits, our sample, in terms of size, lacks the power to detect these influences separately. Standardized estimates of the genetic and environmental variance of *OCD*, *Tics* and *Anxiety disorder* (based on the full ACE model) are presented on the diagonals of Table 3. Familial effects (combining genetic and shared environmental effects) range from 47% (*OCD*) to 61% (*Tics*).

The second set of questions to be examined in the present study concerns associations between OCD and tics, and OCD and anxiety disorders in paediatric community samples. It can be seen in the bottom half of Table 1, first column, that the correlation between the phenotypes *OCD* and *Tics* is 0·32, and that this difference is statistically significant since the lower bound of confidence interval, which is based on χ^2 difference tests at the 0·05 level, exceeds 0. The correlation between the phenotypes *OCD* and *Anxiety disorder* is 0·25, and this is also statistically significant at the 0·05 level. The correlation between the phenotypes *Tics* and *Anxiety disorder* is lower, 0·14, although still statistically significant. Evidence of familial aggregation of the three disorders can be derived from the presence of significant cross-twin cross-trait correlations. The fourth column in Table 1 shows that all these correlations are significant, with the largest aggregations for *OCD* and *Tics* and *OCD* and *Anxiety disorder*. Phenotypic associations may also be expressed in terms of odds ratios (ORs), as follows, with 95% CIs and significance values: *OCD*/*Tics* (OR 4·4, 95% CI 1·3–15·2, $p = 0{\cdot}018$), *OCD*/*Anxiety disorder*

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Table 4. *Genetic (r_g), shared-environmental (r_c) non-shared environmental (r_e) and phenotypic correlation (r_{ph}) (with 95% CI) based on the full ACE model*

	r_g	r_c	r_e	r_{ph} (95% CI)
OCD–Tics	0·30 (0·00–1)	1 (0·00–1)	0·13 (0·00–0·54)	0·31 (0·18–0·44)
OCD–Anxiety disorder	0·26 (0·00–1)	0·78 (0·00–1)	0·02 (0·00–0·29)	0·25 (0·15–0·35)
Tics–Anxiety disorder	0·10 (0·00–1)	0·78 (0·00–1)	0·02 (0·00–0·23)	0·17 (0·06–0·27)

Confidence intervals including zero indicate non-significance.

(OR 2·9, 95% CI 1·0–8·4, $p=0·046$), and *Anxiety disorder*/*Tics* (OR 2·5, 95% CI 1·1–5·7, $p=0·026$). (The contingency tables on which these odds ratios are based are available from the corresponding author.)

The third set of questions to be considered is to what extent familial aggregations of these three conditions are attributable to genetic or shared environmental influences. For this, we look first at the third column of Table 1. Higher MZ compared to DZ cross-twin cross-trait correlations indicate a significant proportion of genetic influences to explain the co-occurrence of the conditions. However, the table shows MZ/DZ cross-twin cross-trait correlations that are quite similar for MZ and DZ pairs, indicating that shared-environmental factors predominantly determine the familial aggregation of conditions.

The first three columns of Table 4 show the A, C and E correlations across disorders (r_g, r_c, r_e), i.e. the extent to which the same A, C and E factors influence the disorders. The off-diagonal elements are a function of r_g, r_c, r_e and the standardized variance components given on the diagonals of Table 3. It can be seen in Table 4 that the genetic (r_g), shared-environmental (r_c) and non-shared-environmental (r_c) correlations for all combinations of symptoms have a zero lower 95% CI, indicating non-significance. This is also the case for the proportions of the phenotypic correlations (r_{ph}) explained by A, C and E (given on the off-diagonals of Table 3). However, formal testing of the combined effects of genetic and shared-environmental correlations (Table 2, models 5–7) showed significant familial aggregation of *OCD* and *Tics* and *OCD* and *Anxiety disorder* [$\Delta\chi^2$ (2 df) = 10·4, $p=0·005$ and 15·2, $p=0·001$ respectively), though not of *Tics* and *Anxiety disorder*. This means that although there is significant familial aggregation between *OCD* and *Tics*, and between *OCD* and *Anxiety disorder* (80% and 97% respectively), we lacked the power to determine the specific sources.

DISCUSSION

Previous estimates of heritability of OCD assessed with symptom scales have suggested modest to moderate additive genetic effects, in a range between 26% and 58%, as reviewed in the Introduction. The present estimate of additive genetic effects of 29% on an OCD phenotype defined in diagnostic terms, but including subthreshold cases, is consistent with the lower end of this range, and the estimate of familial aggregation due to combined additive genetic and shared environment effects, which could not be distinguished in this study, as 47%, is consistent with the upper end of the range of previous estimates.

Evidence for genetic factors in tic disorders has come from reports of high concordance in MZ twin pairs and lower concordance in DZ twins (e.g. Price *et al.* 1985; Hyde *et al.* 1992). The present large-scale twin study in a community sample estimates heritability as 50% for tic disorder syndrome in this population. This estimate is based on a full ACE model in which neither genetic nor shared environmental effects are statistically significant, and the combined effect of both sources of familial aggregation account for 61% of individual variation. Evidence for the validity of the assessment of the phenotype in the present study is that the prevalence estimate for *Tics* of 6·0% (95% CI 4·2–8·4%) is broadly consistent with previous epidemiological studies of tics; for recent review see Scahill *et al.* (2001).

The heritability estimate for the complex phenotype 'any anxiety disorder' is low and not statistically significant. Our recent report on the same sample found high and statistically

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significant additive genetic effects for specific phobia and separation anxiety disorder (Bolton *et al*. 2006). Notwithstanding the fact that in this sample, these two disorders constituted most of the complex category 'any anxiety disorder' inclusion of the rarer anxiety disorders had the effect of substantially reducing familial aggregation and estimate of heritability.

There were significant within-twin associations between OCD and tics, this being the first community population study to replicate this pattern previously found in clinic samples. Significant within-twin associations were also found between OCD and anxiety disorder in this paediatric population, and to a lesser extent between tics and anxiety disorder These phenotypic associations were also found across-twins indexing familial aggregation for *OCD* and *Tics* and for *OCD* and *Anxiety disorder*, but not for *Tics* and *Anxiety disorder*. This pattern of findings is consistent with the hypothesis of a tic-related early-onset OCD phenotype, but also with the hypothesis of an anxiety-related early-onset OCD phenotype, with, however, some overlap between them.

Limitations of the study include that diagnostic interview assessment relied on maternal-informant rather than child-informant or behavioural observation data, which may have led to under-reporting particularly of obsessions and tics. There are also limitations inherent in the twin design and the ACE models for the purpose of heritability estimates. These include chorionicity, atypical gestation of MZ twins, and increased similarity of environment for MZ twins as compared to DZ twins (Martin *et al*. 1997), as well as the inclusion of gene–environment correlations and interactions in the genetic parameter. These limitations are varied in their effects, some resulting in conservative heritability estimates, others resulting in inflated heritability estimates. Finally, study of diagnostically defined phenotypes has the disadvantage that modelling of dichotomous traits has less power than modelling of continuous traits and is less able to distinguish between genetic and shared environmental factors (Neale *et al*. 1994). This limitation affected the modelling in the present study, and it has to be weighed against the advantage of diagnostically defined phenotypes of validity in relation to psychopathology.

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DECLARATION OF INTEREST

None.

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