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Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder

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Abstract

Background—The goals of this prospective longitudinal study were to monitor levels of psychosocial stress in children and adolescents with Tourette syndrome (TS) and/or obsessive-compulsive disorder (OCD) compared to healthy control subjects and to examine the relationship between measures of psychosocial stress and fluctuations in tic, obsessive-compulsive (OC), and depressive symptom severity.

Methods—Consecutive ratings of tic, OC and depressive symptom severity were obtained for 45 cases and 41 matched healthy control subjects over a two-year period. Measures of psychosocial stress included youth self-report, parental report, and clinician ratings of long-term contextual threat. Structural equation modeling for unbalanced repeated measures was used to assess the temporal sequence of psychosocial stress with the severity of tic, OC and depressive symptoms.

Results—Subjects with TS and OCD experienced significantly more psychosocial stress than did the controls. Estimates of psychosocial stress were predictive of future depressive symptoms. Current levels of psychosocial stress were also a significant predictor of future OC symptom severity, but not vice versa. Current OC symptom severity was a predictor of future depressive symptom severity, but not vice versa. Current levels of psychosocial stress and depression were independent predictors of future tic severity, even after controlling for the effect of advancing chronological age.

Conclusions—The impact of antecedent psychosocial adversity is greater on future depressive symptoms than for tic and/or OC symptoms. Worsening OC symptoms are also a predictor of future depressive symptoms. Advancing chronological age is robustly associated with reductions in tic severity.

Keywords

Tourette syndrome; obsessive-compulsive disorder; depression; psychosocial stress; latent variables; longitudinal study

Tourette syndrome (TS) and early-onset obsessive-compulsive disorder (OCD) are etiologically related, chronic, familial neuropsychiatric disorders. These disorders are characterized by intrusive sensory urges, motor and vocal tics, as well as recurrent thoughts and impulses and repetitive behaviors or mental acts that wax and wane in severity (Leckman, 2002). This fluctuation complicates clinical management as well as the interpretation of efficacy and effectiveness of treatment studies. Many studies have emphasized the importance of psychosocial stress in mediating the progression of a number of disease states including headache (Fernandez & Sheffield, 1996), multiple sclerosis (Mohr et al., 2000), human immunodeficiency virus (Evans et al., 1997; Moss, Bose, Wolters, & Brouwers, 1998; Murphy, Moscicki, Vermund, & Muenz, 2000), diabetes (Goldston, Kovacs, Obrosky, & Iyengar, 1995; Thernlund et al., 1995) and major depression (Brown & Harris, 1978; Kendler, Karkowski, & Prescott, 1999; Kendler, Gardner, & Prescott, 2002; Goodyer, Kolvin, & Gatzanis, 1985). Earlier cross-sectional and longitudinal studies of TS and early-onset OCD have consistently suggested that these disorders are sensitive to psychosocial stress (Bornstein, 1990; Chappell et al., 1994; Findley et al., 2003; Hoekstra, Steenhuis, Kallenberg, & Minderaa, 2004; Silva, Munoz, Barickman, & Friedhoff, 1995; Surwillo, Shafii, & Barrett, 1978; Thomsen, 1995).

The goals of this prospective longitudinal study were to monitor levels of psychosocial stress in children and adolescents with TS and/or OCD compared to healthy control subjects and to examine the relationship between measures of psychosocial stress and fluctuations in tic, obsessive-compulsive (OC), and depressive symptom severity. A structural equation modeling framework with latent-time varying constructs was used to maximize the available data obtained at different time points.

Method

Subjects

Subjects in this study were 86 children and adolescents, aged 7 to 17 years, who had been diagnosed with TS alone ($N = 17$), OCD alone ($N = 8$), both TS and OCD ($N = 20$), as well as 41 healthy control subjects (Table 1). As previously described, all patients were being followed at the Yale Child Study Center Tic Disorder/Obsessive-Compulsive Disorder Specialty Clinic (Findley et al., 2003; Lin et al., 2002; Luo et al., 2004). Expert clinicians using *DSM-IV* criteria made all psychiatric diagnoses based on all available information (see below). Exclusion criteria for both groups included an IQ < 75; serious medical illness; major sensory handicaps (blindness, deafness); major neurological disease (including a seizure disorder); head trauma resulting in loss of consciousness; current (past 6 months) psychiatric disorder that could interfere with participation, such as major depression; psychosis; autism or another pervasive developmental disorder. All parents provided written informed consent after the study was described to them in detail. A separate assent form was used to ensure the informed participation of the child and adolescent subjects.

Baseline assessment

When a family entered the study, information concerning the patient was collected in a two-stage process (Findley et al., 2003; Lin et al., 2002; Luo et al., 2004). The first stage consisted of the collection of information concerning symptoms associated with TS and

OCD using a self- and family-report (Tourette Syndrome Association International Consortium for Genetics, 1999) based on the tic inventory and ordinal severity scales of the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989), and the symptom checklist and ordinal scales of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997). In a second stage of assessment, an experienced clinician reviewed these symptom ratings with the child and the parent to ensure their accuracy and validity. Comorbid psychiatric diagnoses, including attention deficit hyperactivity disorder (ADHD), were made using all available information, including data collected using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997). In addition, depression was assessed with the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski, Freeman, & Mokros, 1985), and anxiety was measured with the Revised Children's Manifest Anxiety Scale (RCMAS) (Paget & Reynolds, 1984).

Measurements of psychosocial stress at baseline were made using parent report (Parent Perceived Stress Scale, PSS-P) (Cohen, Kamarck, & Mermelstein, 1983; youth self-report (Daily Life Stressors Scale, DLSS) (Kearney, Drabman, & Beasley, 1993), and a clinician-rated measure of long-term contextual threat (Yale Children's Global Stress Index, YCGSI) (Findley et al., 2003). Normal controls were also assessed for their stress level for comparison with the subjects who had been diagnosed with TS and/or OCD.

Longitudinal ratings

Monthly ratings included an assessment of tic severity by expert raters using the tic portion of the YGTSS. Other monthly ratings included OC symptom severity using the CY-BOCS and the CDRS-R both completed by expert raters. The PSS-P (parental report) was also administered on a monthly basis. The DLSS (self-report) and the clinician-rated YCGSI and CDRS-R were collected every four months. Most subjects completed the monthly visitation schedule during the two-year period, although the number of visits varied among the subjects (min. = 4, max. = 26, mean = 21, median = 24, Scahill et al., 1997).

Medication status

This was a naturalistic prospective longitudinal study of two years' duration; consequently each subject's medication history was monitored each month according to the class of psychotropic agents (adrenergic agonists [clonidine, guanfacine], classical neuroleptics [haloperidol, pimozide, fluphenazine], atypical neuroleptics [risperidone, ziprasidone, olanzapine, aripiprazole], serotonin reuptake inhibitors and other antidepressants [citalopram, clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine], mood stabilizers [lithium, divalproex sodium, topiramate], psychostimulants [methylphenidate, dextroamphetamine], benzodiazepines [clonazepam], other miscellaneous agents). Baseline medication status and changes in medication status were included in the structural equation modeling.

Pathway analyses of the relationship between longitudinal measures of psychosocial stress and tic, OC and depressive symptom severity

The longitudinal design makes it feasible to investigate possible temporal relationships between stress, severity of tic and OC symptoms, and depression. A structural equation modeling framework was employed to explore possible relationships. All the coefficients in a structural equation model are simultaneously estimated via maximum likelihood method with STATA add-on module GLLAMM (Rabe-Hesketh, Skrondal, & Pickles, 2004) since it accommodates different measurement schedules among multiple longitudinal measures. A latent time-varying stress construct (SC) was modeled to represent the underlying true stress level manifested by the three available longitudinal stress measures: the YCGSI, the PSS-P and the DLSS. Time-lag effect was studied with mixed effect submodels in a structural

equation framework by using the nearest recorded past reading of a longitudinal measure as a covariate for a current reading. The effects of previous stress level on current symptom severity and vice versa; the effects of previous stress level on current depression; and the effects of previous depression level on current symptom severity and vice versa were all explored.

Statistical models

Relationships between psychosocial stress and tic, OC and depressive symptom severity were studied via the submodels within the above structural equation modeling framework. Specifically, we developed a latent measure (Stress Construct, SC) of psychosocial stress that was related to each of the three underlying stress measures as specified in the following submodel (Bollen, 1989):

$$S_{ijk} = \gamma_{0k} + \gamma_{1k}\eta_{ij} + \zeta_{ijk}; k=1, 2 \text{ or } 3; \quad (1)$$

where S_{ijk} is the value of type k stress measure recorded at time point j for subject i , γ_{0k} is the corresponding intercept for the type k stress measure that accommodates scale difference in multiple stress measures, γ_{1k} is the factor loading that represents relative contribution of the type k stress measure to the time-varying stress construct η_{ij} at time point j for subject i , and ζ_{ijk} is independently, normally distributed residual with mean zero and variance θ_k^2 . For the sake of model identifiability, the first factor loading γ_{11} is set to one.

The correlations among different stress measures and among different time points of a same measure in a same subject were accommodated by the stress construct η_{ij} that could be affected by other covariates in the following submodel (Bollen, 1989):

$$\eta_{ij} = \alpha^T X_i + \varepsilon_{ij}; \quad (2)$$

where α is a vector of regression coefficients for the corresponding effects of predictors X in subject i , for example, X could include time-lagged measure of depression, and ε_{ij} is the residual that is assumed to follow a multivariate normal distribution with mean zero and covariance of compound symmetry to accommodate within-subject correlations across different time points j .

Finally, the dependence of the longitudinal measures of symptom severity on the SC is described in the following submodel (Bollen, 1989):

$$Y_{ijl} = \beta_{0l} + b_{0il} + \beta_{1l}\eta_{i,j-1} + \beta_{2l}^T Z_{il} + e_{ijl}; \quad (3)$$

where Y_{ijl} is the value of type l symptom severity measure (for example, $l = 1$ for YGTSS, $l = 2$ for CY-BOCS, $l = 3$ for CDRS-R) recorded at time point j for subject i ; β_{0l} is the corresponding fixed intercept; b_{0il} is the corresponding random intercept for subject i that accommodates within subject correlation and is assumed to be normally distributed with mean zero and variance ω_l^2 ; β_{1l} is the regression coefficient for the effect of the time-lagged stress construct $\eta_{i,j-1}$ at time point $j-1$ on type l severity measure for subject i ; β_{2l}^T is a vector of regression coefficients for the corresponding effects of predictors Z_{il} , for example, it can include a time-lagged depression measure for Y_{ijl} of symptom severity or vice versa, and e_{ijl} is the independently, normally distributed residual with mean zero and variance σ_l^2 . The γ 's, α 's and β 's are simultaneously estimated by the GLLMM module in STATA (Rabe-

Hesketh et al., 2004). The effects represented by γ_{1k}, α and β_{1l} are represented by arrow lines. An effect is deemed to be statistically significant if the p -value for Wald test for each of the γ 's, α 's and β 's is smaller than .05.

We also incorporated baseline medication status, a change in medication, and a diagnosis of ADHD as class variables into the longitudinal path models.

Results

Description of study cohort

Distributions of the demographic and clinical variables including age, gender, race, age of symptom onset, and symptom severity scores, stress, anxiety, and depression are presented in Table 1. The sample is a relatively typical group of clinically referred pediatric patients with TS and early onset OCD and age matched healthy control subjects.

Overall stress levels, regardless of the informant, were higher among the TS and/or OCD patients compared to the normal controls (Figure 1). For example, on the blindly rated YCGSI, 47% (21 of the 45) of the patients were judged to be under either a high-moderate or severe level of contextual threat stress on 38 occasions compared to just 20% (8 of 41) of the healthy controls on 17 occasions. Each of the independently determined measures of psychosocial stress was correlated with one another. This was true in both the patient and healthy controls, when the data was analyzed separately by group (data not shown). The parental ratings of perceived stress (PSS-P) were correlated in the range of .65–.67 ($p < .0001$) with each of the other two measures. However, the clinician ratings of long-term contextual threat were only correlated at the level of .43 ($p < .002$) with the subject's self-report of daily life stress (DLSS).

Overall tic symptom severity and obsessive-compulsive symptom severity improved over the 2-year period (Figure 2). Accounting for the longitudinal nature of the tic and OC symptom severity measures, the correlation between YGTSS and CY-BOCS was .34 ($p = .02$). The correlation coefficients between symptom severities of tic (YGTSS) and OC (CY-BOCS) and depression (CDRS-R) were .25 ($p < .001$) and .40 ($p < .001$), respectively. The correlation coefficients between YGTSS and each of the stress measure including PSS-P, DLSS, and clinician ratings in patients were .20 ($p < .0001$), .13 ($p = .023$), and .12 ($p = .037$), respectively. The correlation coefficients between CY-BOCS and each of the stress measures including PSS-P, DLSS, and clinician ratings in patients were .21 ($p < .0001$), .18 ($p = .003$), and .082 ($p = .051$), respectively. The correlation coefficients between depression (CDRS-R) and each of the stress measures including PSS-P, DLSS, and clinician ratings in patients were .60 ($p < .0001$), .37 ($p < .0001$), and .27 ($p < .0001$), respectively.

A minority of subjects were rated as having clinically significant levels of depression (CDRS-R ≥ 40). Specifically, 27% (12 of the 45) of the patients were judged to have a clinically significant level of depression on 20 occasions compared to just 2% (1 of 41) of the healthy controls on a single occasion.

Thirty-nine out of the 45 subjects were taking psychotropic medications at baseline. The treatment of 18 subjects remained unchanged over the entire course of the study (stable medication regimen = 12; and medication free for the duration of the study = 6). At baseline, 13 (29%) subjects were taking neuroleptics, 21 (47%) subjects were on selective serotonin reuptake inhibitors (SSRIs), and 18 (40%) subjects were on alpha agonists. Subjects taking SSRIs had significantly higher baseline ratings of both OC and depressive symptom severity (CY-BOCS ($F [1,41] = 12.03, p = .001$), CDRS-R ($F [1,42] = 10.44, p = .002$). Subjects on alpha agonists had significantly higher baseline ratings of both tic and depressive symptom

severity (YGTSS ($F [1,41] = 5.41, p = .025$), CDRS ($F [1,42] = 8.14, p = .007$). At baseline, no significant differences in tic, OCD, stress or depression scores were observed among the subjects on neuroleptics vs. the remaining subjects.

Exploring relationship between age, stress, depression, tic and OC symptom severity

Increasing chronological age is associated with tic improvement (Figure 3A), e.g., the standardized coefficient of .38 means that following an increase of 2.7 years of age (1 SD of all measures of age in the patient population), we observed a reduction of 38% of 1.0 SD of all the YGTSS scores ($.38 \times 9.0 = 3.4$). Even after controlling for this age effect, current levels of psychosocial stress and depression were still independent and significant (although modest) predictors of future tic symptom severity (Figure 3A). In contrast, current tic severity was not a statistically significant predictor of psychosocial stress or of depressive symptoms (data not shown).

Current stress levels were a robust predictor of future OC symptom severity (Figure 3B). We also observed that current OC symptom severity was a potent predictor of future depressive symptoms (Figure 3B), e.g., the standardized coefficient of .47 means that following an increase of 8.2 units on the CY-BOCS (1.0 SD of all measures of OC symptom severity in the patient population), we estimated an increase of 47% of 1.0 SD of all the CDRS-R scores ($.47 \times 8.7 = 4.1$ units). However, current depressive severity was not a statistically significant predictor of future OC symptoms (data not shown). When the antecedent tic and OC symptom severity ratings were included in the model the effects of psychosocial stress on tic and OC outcomes remained significant, but with reduced effect sizes (data not shown).

Current estimates of psychosocial stress were strongly predictive of future depressive symptoms while current ratings of depressive symptoms were only modestly predictive of future ratings of psychosocial stress (Figure 3C), e.g., the standardized coefficient of .73 means that following an increase of 3.3 units on the PSS-P (1.0 SD on of all measures on the PSS-P in the patient population), we estimated an increase of 73% of 1.0 SD of all the CDRS-R scores ($.73 \times 8.7 = 6.4$ units).

In each of these models the parental report of current stress (PSS-P) was the most robust predictor of stress-related outcomes followed by youth self-report and clinician-rated long-term object threat ratings, in that order.

The severity of anxiety (as measured using the RCMAS) at entry was not statistically related to the severity of tics or OC symptoms recorded over the course of the study (data not shown). Likewise, a diagnosis of ADHD at the entry of the study was not statistically related to the severity of tics or OC symptoms recorded over the course of the study (data not shown). When data concerning changes in a subject's medication status were included as a predictor in Z in submodel (3), there was no influence on the relative significance of the directional findings depicted in Figure 3A, 3B, or 3C (data not shown).

Discussion

As we have reported before, the patient group overall experienced higher levels of stress using all the stress measures than did healthy controls (Bornstein, 1990; Chappell et al., 1994; Findley et al., 2003; Hoekstra et al., 2004; Silva et al., 1995; Surwillo et al., 1978; Thomsen, 1995).

The results from our structural equation modeling framework with latent-time varying constructs support the conclusion that antecedent psychosocial stress, particularly as

perceived by the parent, is a significant predictor of future depressive and OC symptom severity and is a less robust indicator of future tic severity. Our data also indicates that depressive symptoms do predict modest increases in tic severity consistent with earlier predictions (Robertson, Williamson, & Eapen, 2006). Other findings of note include that chronological age has a strong inverse relationship to tic severity.

Still, understanding the interrelationships between tics, OCD, depression, and ADHD is being complicated by the use of cross-sectional designs in most studies of clinically referred subjects. Although the etiological interrelationships between depression and ADHD with TS and OCD have not been fully elucidated, the co-occurrence of these disorders in children and adults with TS or OCD is commonplace and associated with distinctive cognitive profiles, worse social adjustment, increased psychosocial dysfunction, and diminished quality of life (Leckman et al., 1998; Peterson, Pine, Cohen, & Brook, 2001; Bloch et al., 2006; Carter et al., 2000; Dykens et al., 1990; Elstner, Selai, Trimble, & Robertson, 2001; Robertson, Banerjee, Eapen, & Fox-Hiley, 2002; Robertson et al., 2006).

Limitations

These results are from a demographically homogeneous sample of clinically referred TS and OCD patients and might not extrapolate to other populations. On the other hand, our findings are largely consistent with earlier population-based longitudinal studies suggesting the patterns of interactive comorbidity are true over the course of months as well as over the course of years (Peterson et al., 2001).

Given the naturalistic design of this prospective study, we did not formally assess the role of medication on the course of tic, OC and depressive symptomatology. At baseline, however, it appears that medication use may be more a reflection of the treating clinician's perception of which symptoms were the most problematic nature of the presenting symptoms rather than a reflection of the effectiveness of these agents.

Clinical implications

Ratings of psychosocial stress, particularly parent-ratings of perceived stress, appear to be the best predictor of subsequent depressive and OC symptom severity and a modest predictor of tic severity. This suggests that parental perceptions of child stress are a worthwhile variable to monitor. It is surely a cost-effective variable given the considerable resources needed to determine the long-term contextual threat associated with stressful life events compared with simply asking a parent the four questions on the PSS-P. The magnitude of these effects can be estimated by the standardized coefficients such that an increase of 1.0 standard deviation (SD) on the PSS-P is estimated to increase the future ratings of depressive symptoms by 6.4 units on the CDRS-R (four months later, Figure 3). Similarly, an increase of 1.0 SD on the CY-BOCS is estimated to increase the future ratings of depressive symptoms by 4.1 units on the CDRS-R (four months later). To place these changes in context, depressed adolescents treated with a combination of cognitive behavioral therapy and fluoxetine on average improved by 27.0 units on the CDRS-R over the course of a three-month clinical trial (March et al., 2004). Alternatively, an increase of 1.0 standard deviation (SD) on the PSS-P is estimated to increase the future ratings of OC symptoms by 6.4 units on the CY-BOCS (one month later).

We found a clear relationship between future depression ratings and antecedent ratings of psychosocial stress. In contrast to earlier adult studies (where long-term contextual threat ratings have consistently been found to be the most powerful predictor of depression) (Brown & Harris, 1978; Kendler et al, 1999; Kendler et al., 2002; Kendler, Kuhn, & Prescott, 2004), we found that the level of psychosocial stress as perceived by the patient

(usually the mother) was the most predictive. Although this conclusion is constrained by the number of cases who were seriously depressed during the course of the study, it is important for clinicians working with children and families to be sensitive to the importance of parental perception of psychosocial stress and the future course of tic and OC symptoms as well as depression.

Clinically it is also important to note that these findings replicate and extend earlier studies with regard to the natural history of tic disorders where age 9–12 is an inflection point beyond which tic severity gradually declines in a majority of cases (Leckman et al., 1998; Bloch et al., 2006; Coffey et al., 2004). To further contextualize these findings, we note that in a group of 33 children and adolescents with TS and ADHD randomized to treatment with a combination of clonidine and methylphenidate, the total tic score on the YGTSS on average improved by 12.0 units over the course of a four-month clinical trial (The Tourette's Syndrome Study Group, 2002). Overall, these findings provide an optimistic long-term outlook for parents and children beset with severe and worsening tics in preadolescence.

However, the presence of comorbid ADHD is another important consideration if clinicians are to provide the best possible care for these complex cases given its potential adverse impact on the developmental course of children and adolescents (Peterson et al., 2001; Bloch et al., 2006; Carter et al., 2000; Dykens et al., 1990; Stokes, Bawden, Camfield, Backman, & Dooley, 1991; Sukhodolsky et al., 2003, 2005). This is especially true when multiple comorbidities occur in the same child. The presence of multiple coexisting conditions is likely to magnify the level of stress the family is experiencing and create negative multidirectional interactions within the family and peer group as well as further jeopardize academic performance.

Future directions

The pathogenesis of TS and early-onset OCD remains in doubt. In addition to chronological age and psychosocial stress, recent attention has focused on genetic factors (Abelson et al., 2005), the possible role of post-infectious autoimmune mechanisms (Leckman et al., 2005), and the development of basal ganglia structures (Kalanithi et al., 2005; Bloch, Leckman, Zhu, & Peterson, 2005). Future prospective longitudinal studies are needed to deepen our understanding of the role of psychosocial stress and its interaction with genetic vulnerability factors and immune function to influence the course of brain structure and function to produce the broad range of outcomes typical of these of these complex disorders.

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Abbreviations

TS	Tourette syndrome
OCD	obsessive-compulsive disorder

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Figure 1.

Group-specific stress measures. Stress scores at each time point (Baseline = TB, visit 4, 8, 12, 16, 20, 24 months after baseline = T4, T8, T12, T16, T20, T24, respectively) over the two-year period were averaged separately across patients and controls. Stress scores are plotted for Perceived Stress Scale – Parent (PSS-P), Daily Life Stressors Scale Parent (DLSS), and Yale Children's Global Stress Index (YCGSI). Stress levels for all the three stress ratings PSS-P, DLSS, and YCGSI over the two-year period are significantly higher among the patients with TS and/or OCD than those among the normal controls ($Z = 6.97$, $p < .0001$ for PSS-P; $Z = 3.95$, $p < .0001$ for DLSS; and $Z = 2.84$, $p = .0045$ for YCGSI)

Figure 2. Trajectories of YGTSS and CY-BOCS. Yale Global Tic Severity Scale (YGTSS) and Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) symptom severity scores are plotted among the patients over the two-year period (TB to T24)

Figure 3.

Pathway analyses of the relationships between longitudinally collected measures of psychosocial stress and tic, obsessive-compulsive (OC) and depressive symptom severity. Squares depict measured variables and circles represent latent variables. The standardized coefficients represent the size of the effects and the p -values in parentheses represent the significance of these effects as a result of the Wald test. An effect is deemed to be statistically significant if the p -value for the Wald test for each of the γ 's, α 's and β 's is smaller than .05 (see text). The standardized coefficients are the proportion of 1.0 standard deviation (SD) of the predicted variable that can be explained by 1.0 SD change in the predicting variable. A solid line indicates a statistically significant positive relationship; a dashed line indicates a significant inverse relationship. The thickness of the lines reflects the relative significance of the interactions. An arrow indicates a predictive relationship, while a line without an arrow head indicates the relative contributions to a latent variable. (A) **Tic symptoms.** In this model, future tic improvement was associated with advancing chronological age. The standardized coefficient of .38 means that following an increase of 2.7 years of age (1 SD of all measures of age in the patient population), we observed a reduction of 38% of 1.0 SD of all the YGTSS scores ($.38 \times 9.0 = 3.4$). In addition, increases in past depressive symptoms (Children's Depression Rating Scale-Revised, CDRS-R_{T-1}) predict higher levels of current psychosocial stress (Stress Construct, SC), which in turn modestly, but significantly, predict increases in future tic severity (Yale Global Tic Severity Scale, YGTSS_{T+1}). Increases in current depressive symptoms (Children's Depression Rating Scale-Revised, CDRS-R_T) are also modestly, and independently, predictive of increases in future tic symptom severity (YGTSS_{T+1}). Prior tic symptom severity (YGTSS_{T-1}) does not affect current depressive symptom ratings; and past YGTSS scores also do not significantly affect current stress levels (data not shown). The SC is a latent variable derived from the Yale Children's Global Stress Index (YCGSI), the Perceived Stress Scale-Parent (PSS-P) and the Daily Life Stress Scale (DLSS). (B) **Obsessive-compulsive (OC) symptoms.** Higher levels of psychosocial stress in the past (SC_{T-1}), predict higher levels of current obsessive-compulsive symptom severity (Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS_T]), which subsequently predicts future depressive symptom severity (CDRS-R_{T+1}). The standardized coefficient of .47 means that following an increase of 8.2 units on the CY-BOCS (1.0 SD of all measures of OC symptom severity in the patient population), we estimated an increase of 47% of 1.0 SD of all the CDRS-R scores ($.47 \times 8.7 = 4.1$ units). (C) **Depressive symptoms.** The previous (time-lagged) depressive symptom severity (CDRS-R_{T-1}) strongly predicts current levels of psychosocial stress (SC), which subsequently predicts future levels of depressive symptoms (CDRS-R_{T+1}). The standardized

coefficient of .73 means that following an increase of 3.3 units on the PSS-P (1.0 SD of all measures on the PSS-P in the patient population), we estimated an increase of 73% of 1.0 SD of all the CDRS-R scores ($.73 \times 8.7 = 6.4$ units)

Table 1

Demographic and clinical characteristics at baseline

Variable	<i>n</i>	Tic/OC patients (<i>N</i> = 45)	<i>n</i>	Unaffected controls (<i>N</i> = 41)
Age in years (SD), range	45	12.0 (2.7), 7.5–16.9	41	12.7 (2.7), 7.5–17
Sex (% female)*	11	24%	20	49%
Ethnicity (%Caucasian)	42	93%	34	83%
Parent education in years (SD)	44	15.2 (2.0)	41	15.6 (2.1)
Age of onset (SD), range				
TS (including chronic tics)	37 ^a	5.9 (2.3), 2–12	NA	NA
OCD	28 ^b	7.4 (3.0), 3–13		
Baseline symptom severity by diagnosis				
TS (including chronic tics) ¹	37 ^a	15.4 (8.1), 0–34	NA	NA
OCD ²	28 ^b	12.8 (7.9), 0–29		
Stress characteristics at baseline				
Perceived Stress Scale Parent (PSSP)**	44	6.5 (3.1), 2–13	38	2.8 (2.0), 0–8
Daily Life Stressors Scale (DLSS)**	45	15.3 (12.6), 0–58	40	4.7 (5.5), 0–24
Yale Children's Global Stress Index (YCGSI)	43	1.8 (1.1), 0–4	38	1.7 (1.1), 0–3.75
ADHD at baseline (%)	26	58%	NA	NA
Anxiety ^c (SD), range**	43	10.2 (6.5), 0–25	40	3.8 (4.2), 0–19
Depression ^d (SD), range**	45	26.4 (7.9), 17–48	41	18.1 (1.5), 17–24

TS = Tourette syndrome, OCD = Obsessive-compulsive disorder, NA = Not applicable.

¹Total tic severity score on the YGTSS (Yale Global Tic Severity Scale), range 0–50.

²Total score on the CY-BOCS (Children's Yale-Brown Obsessive-Compulsive Scale), range 0–40.

³Combined scores on the YGTSS and CY-BOCS, range 0–90.

^aNumber of subjects out of 45 patients who had TS (including chronic tics).

^bNumber of subjects out of 45 patients who had OCD.

^cRaw score on the Revised Children's Manifest Anxiety Scale (RCMAS), range 0–28. *T* scores were used for data analysis purposes.

^dTotal score on the Children's Depression Rating Scale – Revised (CDRS-R), range 17–113

Significant differences between Tic/OCD patients and unaffected controls:

* $p < .05$;

** $p < .0001$.