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ARTICLE

Longitudinal Course of Anxiety in Children and Adolescents With Williams Syndrome

JANET WOODRUFF-BORDEN,* DORIS J. KISTLER, DANIELLE R. HENDERSON, NICOLE A. CRAWFORD, AND CAROLYN B. MERVIS

The longitudinal course of anxiety disorders in 45 children and adolescents with Williams syndrome (WS) was examined. Children were ages 4–13 years at the initial assessment. To assess their child's DSM-IV diagnoses, parents completed a structured diagnostic interview 3–9 times at intervals of at least 1 year. At the first assessment, 60% of the sample presented with at least one anxiety diagnosis; 82.2% received an anxiety diagnosis at some time during the study. Chronic, persistent anxiety within the period 5 years after their initial diagnosis was shown by 62.2% of those with an anxiety diagnosis (51.1% of the entire sample). The most common diagnoses were specific phobias and generalized anxiety disorder. Multilevel logistic regression models were estimated for the presence of any anxiety disorder, specific phobia, and specific phobia of loud noises. Developmental trajectories, expressed as the probability of a positive diagnosis, suggested that the odds of a positive diagnosis did not change with age. IQ was not significantly related to the presence of an anxiety disorder. However, there was a significant relation between executive functioning and anxiety such that the presence of an anxiety diagnosis was associated with increased scores on behavioral regulation, indicative of increased difficulty with inhibitory control of affect and behavior. These findings are discussed in terms of persistence of anxiety over time and the need to develop and test interventions to address the high levels of anxiety experienced by children and adolescents with WS.

KEY WORDS: Williams syndrome; anxiety; intellectual disability; developmental trajectory; executive function

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INTRODUCTION

Williams syndrome (WS) is a neurodevelopmental disorder caused by deletion of approximately 25 genes on chromosome 7q11.23 [Hillier et al., 2003]. Prevalence is estimated at 1 in 7,500 live births [Strømme et al., 2002]. WS has been associated with specific medical, cognitive, and behavioral phenotypes. Medically, the syndrome is associated with mild to moderate intellectual disability, connective tissue abnormalities, characteristic facial features, hypercalcemia, failure to thrive in infancy, cardiovascular disease (particularly supravalvar aortic stenosis), and decreased muscle tone in children [Pober and Dykens, 1996; Morris, 2006]. The cognitive phenotype is characterized by relative strengths in concrete language and verbal short-term memory [Mervis et al., 2000; Mervis and John, 2009] and significant weakness

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in visuospatial construction [Bellugi et al., 2000; Mervis et al., 2000; Mervis and John, 2009]. Behaviorally, individuals with WS have been described as gregarious, friendly, empathetic, and loquacious [von Arnim and Engle, 1964; Jones et al., 2000; Klein-Tasman and Mervis, 2003; Zitzer-Comfort et al., 2007; Järvinen-Pasley et al., 2008].

Anxiety and fearfulness are also significant aspects of the behavioral phenotype of WS [Einfeld et al., 1997, 1999, 2001; Dykens, 2003; Leyfer et al., 2006, 2009; Porter et al., 2009]. Below, we review the literature to date on the prevalence of anxiety in individuals with WS, cohort studies of anxiety at different ages of individuals with WS, and what is known thus far about the persistence of symptoms over time in individuals with WS. Together, this literature establishes both that anxiety in an important component of the phenotype of WS and that symptoms of anxiety persist over time. We also briefly review the course of anxiety over time in individ- uals in the general population (GP). The current study extends previous research on anxiety in individuals with WS by examining whether diagnostically sig- nificant levels of anxiety are present longitudinally in a sample of children and adolescents with WS. The distinc- tion between the presence of symptoms and the presence of symptoms meeting diagnostic thresholds is important as diagnoses require a constellation of symptoms plus interference and distress, as well as the potential need for inter- vention. Thus, the current study pro- vides the first longitudinal data on the developmental trajectory of diagnoses of anxiety in WS.

Prevalence of Symptoms of Anxiety in Williams Syndrome

Studies of behavioral characteristics of children with WS consistently find elevations in symptoms of anxiety. For example, Klein-Tasman and Mervis [2003] compared personality features of 8–10-year-olds with WS to a CA- and IQ-matched group of children with developmental disabilities (DDs) of mixed etiologies. Children with WS

were significantly more tense than the comparison group. Udwin and Yule [1991] also found that children with WS had higher levels of behavioral and emotional problems, especially anxiety, in comparison to a sample matched on CA, SES, and verbal IQ.

Dykens [2003] presented three studies examining fears and anxiety in individuals aged 6–48 years with WS. In the first two studies, parent- and self- report of fears were examined. Results of both studies supported prior findings of elevated anxiety and fears. Individuals with WS had significantly higher scores on the Fear Survey Schedule for Children-Revised [FSSC-R; Ollen- dick, 1983] total and all five factor scores in comparison to a matched mixed etiology control group. Examination of the content of fears in both groups suggested some differences by age, with adults and adolescents reporting more fear of criticism and death/danger than did children. There was also an interaction of age and gender, with female adults and adolescents in comparison to female children reporting greater fears of injury and small animals. Although the cohort design precluded examination of the actual course of the fears, it appeared that fears were found across different ages in individuals with WS but that their content may shift somewhat. In the third study, the first to use a DSM-based interview to examine rates of diagnostic levels of phobias and other anxiety disorders, the Diagnostic Interview Schedule for Children-Parent [DICA- P; Reich et al., 1991] was administered to parents/caregivers of 51 individuals with WS, ages 5–49 years. Results suggested that many of these fears may reach diagnostically significant levels. Based on DSM-III-R criteria, 35% of the sample met criteria for a specific phobia. In addition, 16% of the sample met diagnostic criteria for overanxious disorder, 4% for separation anxiety disorder, and 2% for obsessive compul- sive disorder.

Two research groups have con- ducted diagnostic studies in which all of the participants were adults. Cherniske et al. [2004] studied a group of adults with WS over the age of

30 years. Nineteen of the 20 participants were described as having clinically sig- nificant problems with anxiety. Of the 18 interviewed with a standard diagnostic interview, 13 were diagnosed with moderate to severe anxiety, most often specific phobias or generalized anxiety (frequencies not reported). Stinton et al. [2010] administered the Psychiatric Assessment Schedule for Adults with DDs [PAS-ADD; Moss et al., 1996] to the caregivers of 92 19–55-year-olds with WS. The PAS-ADD provides ICD-10 diagnoses of mental health problems, including anxiety dis- orders. Based on a screening interview, 75 (83%) were identified as having at least one mental health problem.

Two of these individuals did not have sufficient linguistic ability to complete the PAS- ADD. The remaining 73 completed this interview, as did caregivers of all 75 individuals. Fifteen people (16.5% of the total sample) met diagnostic criteria for at least one anxiety disorder, with the most common being specific phobia (12% of the total sample). Other anxiety diagnoses included agoraphobia (four individuals), panic disorder (three indi- viduals), social phobia (two individuals), and generalized anxiety disorder (one individual). Mean IQ was almost iden- tical for individuals who had mental health problems and those who did not. The authors noted that both specific phobias and generalized anxiety disor- ders may have been under-diagnosed by the PAS-ADD.

Three studies addressing anxiety diagnoses have focused on children and adolescents with WS. Leyfer et al. [2006] examined the prevalence of anxiety disorders in 119 children and adolescents with WS aged 4–16 years based on DSM-IV criteria. Use of an interview specifically designed for children and adolescents that is based on current diagnostic criteria allowed careful examination of the rates of diagnostic levels of anxiety. Based on the Anxiety Disorders Interview Schedule for DSM-IV: Parent version [ADIS-P; Silverman and Albano, 1996], Leyfer et al. found that the most prevalent disorder was specific phobia (54% of the sample), followed by generalized anxiety

disorder (12%), separation anxiety (7%), and OCD (3%). Kennedy et al. [2006] also used the ADIS to diagnose anxiety disorders in 21 individuals with WS aged 7–28 years (mean age 16 years). Ten individuals (48%) received at least one anxiety diagnosis, with the most com- mon being specific phobia (43% of the total sample). Other anxiety diagnoses included generalized anxiety disorder (24%), separation anxiety (5%), panic disorder (5%), agoraphobia (5%), and post-traumatic stress disorder (5%). Ley- fer et al. [2009] compared the prevalence of anxiety disorders in 132 4–16-year- olds with WS to that reported in epidemiological studies of children from the GP [Shaffer et al., 2000] and from a population with DDs [Dekker and Koot, 2003]. Children with WS were found to have significantly higher rates of specific phobias [56.1% (WS); 1.3% (GP); 6.8% (DD)], generalized anxiety [7.6% (WS); 3.1% (GP); 0% (DD)], and separation anxiety [6.1% (WS); 2.3% (GP); 1.9% (DD)].

Course of Symptoms of Anxiety Over Time

Together, the literature has established the prevalence of anxiety, both at the symptom and diagnostic levels, in individuals with WS. Several studies have also examined the course of anxiety symptoms over time. Switaj [2000] used parental report measures to examine the course of anxiety behaviors and traits in a cohort design of 190 children, divided into ages 6–9, 10–13, and 14–18 years. On most measures, the oldest group or two older groups scored higher than the youngest group, suggesting that anxiety may increase with age. Leyfer et al. [2006] examined the stability of anxiety diagnoses across time in a cohort design. The sample was divided into three age groups, 4–7, 8–10, and 11–14 years. Prevalence of specific phobias did not differ across the age groups. However, relative to the overall prevalence of generalized anxiety in the WS sample, the prevalence for the youngest group was significantly lower than expected and the prevalence for the oldest group was significantly higher than expected.

Einfeld and colleagues have con- ducted a series of studies examining the longitudinal course of behavioral and emotional problems in individuals with WS. Einfeld et al. [1997] compared emotional difficulties in 70 children and adolescents with WS to those of an epidemiological control group. After statistically controlling for age, gender, and level of intellectual disability, the WS group was found to score significantly higher on overall levels of emotional and behavioral problems, anxiety, and com- munication difficulties. The proportion of individuals exceeding the cutoff for probable psychiatric diagnosis was also significantly greater in the WS group (61.4% vs. 40.7%). In two follow ups to the 1997 study, Einfeld et al. [2001; Time 2] and Tonge and Einfeld [2003; Time 3] examined the persistence of symptoms over time. Five years (Time 2) after the initial assessment, individuals with WS continued to show evidence of emo- tional and behavioral problems, com- munication difficulties, and anxiety. Eight years after the initial assessment (Time 3), total behavior problems in the WS group decreased somewhat, although they were still higher than in the comparison sample. The WS group continued to have higher levels of communication difficulties but no lon- ger showed significantly greater levels of anxiety. The WS group also had signifi- cantly more behavior problems than a matched epidemiological control group and a matched fragile X syndrome group, but the same level as a matched Prader–Willi syndrome group [Einfeld et al., 1999; Einfeld, 2005]. Together, these studies demonstrate that behavio- ral and emotional problems are not only prevalent in children with WS but also may persist over time. Einfeld et al.'s results also suggest that these problems may reach the level of diagnostic significance.

Normative Course of Anxiety in Childhood

Anxiety is considered a normative feature of development, with children progressing through what are considered developmentally appropriate stages of

anxiety [Beidel and Stanley, 1993; Woodruff-Borden and Leyfer, 2006]. In general, both the content and level of abstraction of anxiety and fears tend to change over time, with a shift from concrete, physical threats to more abstract ones as the capacity for abstract thinking develops [Vasey, 1993]. It is critical to distinguish between transient experiences of childhood and adoles- cence and those symptoms that are of sufficient significance to cause distress and interference—and thus be diagnos- tically significant. For the large majority of children, anxiety is a transient experience that does not rise to the level of diagnostically significant anxiety. For those children who are

diagnosed with an anxiety disorder, the course of the disorder tends to be relatively unstable over time. For example, Beidel et al. [1996] followed anxious children for 6 months and found that while most remained anxious, their specific diag- nosis changed. In a prospective study, Last et al. [1996] followed children and adolescents, ages 5–18 years, 3–4 years after their initial diagnosis of an anxiety disorder. Eighty-two percent of the sample no longer met criteria for their initial remission diagnosis, within with the first 2

3

of year. the Although sample in

31% of the sample met criteria for a specific phobia at the initial assessment, by follow-up only 9.45% met criteria for specific phobia. At follow up, 30% of the full sample had developed a new psychi- atric diagnosis, including 16% with a new anxiety diagnosis. These findings suggest that the stability of any specific anxiety diagnosis tends to be rather low in typically developing children, whereas the stability of a diagnosis of any anxiety disorder is somewhat higher. These findings provide a point of comparison to the stability of diag- nostic levels of anxiety in children and adolescents with WS.

Current Study

In sum, literature to date has demon- strated that symptoms of anxiety and diagnostic levels of anxiety are highly prevalent in individuals with WS and exceed rates seen in either the GP or

epidemiological samples of children with DD. Cohort studies of individuals with WS show that the anxiety is present across age groups, and perhaps even more critically, results from longitudinal studies indicate that symptoms of anxiety in WS persist over time. The question of whether clinically significant diagnostic levels of anxiety similarly persist has not been previously addressed, however. Further, the stabil- ity of anxiety diagnoses tends to be relatively low over time in typically developing children. The purpose of the current study was to examine the longitudinal course of clinically signifi- cant levels of anxiety over time in children and adolescents with WS. That is, once anxiety is diagnosed in a child with WS, is the course chronic or are there changes over time? Given the cohort findings of age differences in rate of generalized anxiety, we also examined the course of each diagnosis over time. In addition, we addressed the question of whether there was a relation between the presence or absence of an anxiety diagnosis and either IQ or executive functioning, controlling for CA, both at the initial assessment and over time.

METHOD

Participants

Participants were 45 children (24 girls, 21 boys) with genetically confirmed WS. All of the participants were enrolled in an ongoing longitudinal study of cognitive and language development of individuals with WS conducted at the University of Louisville. The age at first assessment ranged from 4.00 to 13.42 years, with a mean of 6.67 years (SD1⁄42.89 years). The age at the most recent assessment ranged from 6.02 to 16.95 years with a mean of 10.82 years (SD1⁄43.04). The median age over all assessments was 8.9 years.

As part of the larger study, the ADIS-P was administered to the parent of every child participant aged 4 years or older each time the child was assessed. Children were included in the current study if their parent had completed the ADIS-P interview at least three times.

The mean number of assessments per child was 4.91 (range: 3–9; SD1⁄41.74).

Measures

ADIS-P [Silverman and Albano, 1996]. The ADIS-P is a semi-structured inter- view designed to assess anxiety and related disorders in children and adoles- cents (through age 16 years). The inter- view is based on DSM-IV criteria and, in addition to diagnosis, severity ratings from 0 (absent) to 8 (severe) are given for each diagnosis. The ADIS-P has excel- lent reliability for separation anxiety disorder, social phobia, specific phobia, and generalized anxiety disorder, as well as excellent test–retest reliability of the interview [Silverman et al., 2001]. Although the validity of the ADIS-P has not been reported in samples of children with WS, use of DSM criteria for individuals with mild to moderate intellectual disability is widely accepted [e.g., Brown et al., 2004].

All interviewers were required to meet reliability criteria of three succes- sive matches with training tapes and one final interview reviewed by a licensed clinical psychologist on all diagnoses and severity ratings within one point before conducting interviews. Interviewers were advanced clinical psychology doc- toral students or licensed clinical psy- chologists. All interview protocols were reviewed with the supervising clinical psychologist. Diagnostic disagreements were resolved through discussion. Con- sistent with DSM criteria, an anxiety disorder was diagnosed only if it caused both interference and distress.

Kaufman Brief Intelligence Test, second edition [KBIT-2; Kaufman and Kaufman, 2004]. The KBIT-2 is an individually administered intellectual ability assessment normed for ages 4– 89 years, yielding a Verbal standard score, Nonverbal Reasoning standard score, and composite IQ (mean1⁄4100, SD1⁄415).

Behavior Rating Inventory of Executive Functioning [BRIEF; Gioia et al., 2000]. The BRIEF is an 86-item questionnaire for parents of 6–18-year- olds regarding executive functioning behaviors in home and at school. The

BRIEF includes eight scales and yields two summary indices and an overall composite, each reported as a T-score (mean1⁄450, SD1⁄410, lower scores indi- cate higher ability). The Behavioral Regulation Index (three scales)

measures the ability to shift cognitive set and to use inhibitory control to monitor both emotions and behavior. The Metacog- nition Index (five scales) measures the ability to actively solve problems across a variety of contexts by initiating, planning, organizing, and maintaining future-oriented problem solving in working memory. The Global Executive Composite is a summary measure that incorporates all 8 scales.

Data Analysis Strategy

Our aim was to model within-person change over the study period in the presence of any DSM-IV anxiety diagnosis as measured by the ADIS-P. We also modeled within-person change in the presence of any DSM-IV specific phobia diagnosis (the most common anxiety diagnosis for children with WS; e.g., Leyfer et al. [2006]) and in the DSM-IV specific phobia of loud noises diagnosis (the most common specific phobia diagnosis for children with WS; e.g., Leyfer et al. [2006]). We also assessed the relations between these diagnoses and measures of executive function (BRIEF BRI and MI) and IQ (KBIT-2 Composite IQ). We used multilevel modeling techniques [Raudenbush and Bryk, 2002; Singer and Willett, 2003] to estimate models that include both estimates of individual change over time and inter-individual variability in change trajectories. Multi- level modeling provides a flexible and powerful method to model develop- mental change in longitudinal data and has been used extensively with data that tend to be normally distributed (e.g., height, IQ). These techniques can also be applied to binary data (e.g., presence/ absence of a disease), although there are considerably more statistical complica- tions [Hu et al., 1998; Carlin et al., 2001; Neuhaus, 2001].

When analyzing longitudinal data, it is important to account for the

statistical dependencies or correlations in repeated observations of the same per- son. Multilevel models accomplish this by specifying models at different hier- archical levels to characterize growth (or decline). For a two-level model, the Level 1 model describes individual (within-person) change over time. The Level 2 model describes inter-individual (between-person) variability in the change trajectories defined by the parameters of the Level 1 model. In the simplest Level 1 model, individual change over time would be character- ized by a linear model which includes only an intercept, typically an indicator of initial status or status at a fixed age, and a slope (change) parameter. The Level 2 model is formulated to account for individual differences in the intercepts and slopes estimated for each individual at the first level. For example, predictors such as gender or socioeconomic status might be introduced at Level 2 to account for individual variability in intercepts and in slopes. (See Singer and Willett [2003] for detailed concep- tual and mathematical accounts of multi- level modeling of longitudinal data.)

A major advantage of multilevel modeling is the capacity to handle unbalanced designs. In an unbalanced design, age at the initial measurement and measurement intervals can vary. The data described here constitute an unbal- anced design since participants entered the study at different ages. As a first step, models were formulated to determine whether within-person change was independent of the initial age differences [Miyazaki and Raudenbush, 2000; Neu- haus, 2001]. Since there was no evidence of a relation between initial age and within-person change (data not shown), simpler models focusing on within- person change were tested.

One of the first steps in multilevel modeling is to determine the shape of the function defining the within-person change over time (i.e., the Level 1 model). In many cases a linear model is adequate to model change over a limited age range or time period. For example, to model the change in IQ as a function of chronological age (CA) and anxiety diagnosis, the Level 1 model, which

estimated an intercept (predicted score at age 9 years) and slope (annual rate of change) for each participant, is specified in the equation below:

$$\hat{Y}_{ti} = \pi_{0i} + \pi_{1i}(CA_{ti} - 9) + \pi_{2i} X_{ti} + e_{ti} \quad (1)$$

In the Level 1 equation, $\hat{Y}_{ti}$ repre- sents the predicted KBIT-2 Composite IQ score for person i at CA t and X_{ti}

is person i's anxiety diagnosis (present or absent) at CA t. The median age of 9 years was subtracted from CA. This procedure, which is referred to as centering age, is recommended because it enables a more meaningful interpre- tation of the intercept and often increases the stability of the model estimation [Raudenbush and Bryk, 2002; Singer and Willett, 2003]. The parameters p

0i and p

1i

are each individual's intercept and linear CA slope. The effect of anxiety is indicated by p

2i

and is a time-varying parameter. The residual error term e

ti

indicates the amount of error in predicting the person's IQ at a given CA, controlling for the anxiety diagnosis.

In the Level 2 model, the individual parameter estimates from the Level 1 model are the outcome variables and the model is formulated to determine if there is significant inter-individual var- iability in the developmental trajecto- ries. The Level 2 model typically includes an equation for each Level 1 parameter:

p

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where b

k

is the average, over individuals, for each of the k parameter estimates. Additionally time-invariant predictors such as gender could be included in the Level 2 models as explanatory variables. The parameter averages are also referred to as fixed effects and each can be evaluated by a significance test. The r

ki are person-specific (e.g., intercept) resid- uals and are assumed to be normally distributed about their respective aver- ages with variances, s

k

2. These variances represent the random effects of the model and are estimates of between-person variability or individual differences.

The multilevel logistic regression can be used to assess developmental change for longitudinal dichotomous data such as the presence or absence of any anxiety diagnosis. This approach is particularly useful when individual differences are considered important as compared to methods which estimate ''population- average'' effects, treating between-per- son and within-person effects as indis- tinguishable [Hu et al., 1998]. The Level 1 model is:

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where p

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is the predicted probability of a positive diagnosis and p

0

and p

1

are the intercept and slope. In this model the intercepts are allowed to vary among individuals. The Level 2 model for the intercept p

ki

is identical to Equation (2). The Level 2 model for slopep

ki

estimates a common slope for all individuals. The intercept fixed effect, b

0

, represents the log odds of a positive diagnosis for the average individual (i.e., r

ki

1⁄40) and the slope, b

1

, estimates the annual rate of change in the log odds.

The software package HLM 6.0 [Raudenbush et al., 2004] was used to fit the multilevel models. The models were fit using restricted maximum likelihood estimation. For the multilevel logistics models, unit-specific estimates of fixed effects with robust errors are reported.

RESULTS

Rate of Anxiety in the Sample

The presence of anxiety at the first ADIS-P administration was examined. Of the 45 children, 27 presented with

at least one anxiety diagnosis at their first assessment, translating to a rate of 60%. Next, we examined the rate of anxiety diagnosed at any time during the period the child was assessed. A total of 37 children (82.2% of the sample) met diagnostic criteria for at least one anxiety disorder at some point during the study.

Persistence of Anxiety

To control for the different numbers of assessments across children, we

operationally defined persistence as an anxiety diagnosis present in at least 50% of all assessments subsequent to the initial diagnosis. Of the 37 children diagnosed with anxiety at some time during the study, 62.2% (51.1% of total sample) showed chronic, persistent anxiety. Thus, once a child with WS experiences clinically significant anxiety, the normative course is for the anxiety and its associated distress to persist over time.

As shown in Table I, the most common diagnoses were specific pho- bias and generalized anxiety disorder. For each diagnostic category, we exam- ined the proportion of children con- tinuing to meet diagnostic criteria within the period 5 years after their initial diagnosis. The proportion of children continuing to experience diag- nostic levels of anxiety was considerable. As shown in Table I, 74% of those with a phobia of loud noises continued to have that fear during the 5 year period; 63% with other specific phobias also showed chronicity of their fear. Blood-injury-injection phobias also tended to persist over time. Interestingly, there was more variability in animal phobias and gener- alized anxiety. In part, this appears due to the range of ages for the initial diagnosis.

Table II illustrates the diagnostic profile for each child. Of note is the variability in timing of diagnosis of each disorder. Despite the relatively small sample size, it is clear that anxiety is prevalent, but that the type of anxiety does

not appear related to age per se. Rather, it is apparent that once a child with WS is diagnosed with anxiety, the probability of his or her developing additional anxiety disorders is quite significant. Of those children with anxiety, 26 of 36 (72.2%) developed additional anxiety disorders diagnosed at assessments subsequent to the initial diagnosis of anxiety. One participant was excluded from this analysis because anxiety was first diagnosed at the most recent assessment, precluding a test of the subsequent development of anxiety in this case. Thus, using a total sample of 36 anxious children, we calculated the prob- ability of diagnoses of anxiety subsequent to the first diagnosis. Last et al. [1996] reported that 16% of their prospective clinical sample of typically developing children developed at least one additional anxiety diagnosis after the initial assess- ment. Using 0.16 as the probability that a child will develop an additional anxiety diagnosis beyond that identified in an initial assessment, the identified propor- tion for the WS sample of 0.72 is significantly greater than the predicted probability, as indicated by a binomial test ($P<0.00001$). The WS probability of 0.72 also significantly exceeds that of a chance 0.50 probability (yes/no additional diagnoses; $P<0.011$). Additionally, the presence of one specific phobia appears to increase the likelihood of diagnosis of additional specific phobias. The frequency of additional diagnoses suggests general- ization of anxiety over time.

We also examined the rate of treat- ment for anxiety in the sample. Thirteen

children were medicated at some point in the study for anxiety (28.9% of the total sample). Of these, nine (or 69.2% receiv- ing medication) continued to meet the operational definition of chronic anxiety; three were not diagnosed during the study as anxious; and one was diagnosed as anxious, but not chronically so. A total of eight children received psychotherapy for anxiety (17.8% of the total sample). Of these, six (or 75% of those receiving therapy) continued to meet the opera- tional definition for chronic anxiety whereas two were not diagnosed as anxious during the study.

Multilevel Logistic Regression Models

Multilevel logistic regression models were estimated to evaluate the change over time in the presence of any anxiety disorder, specific phobia, and specific phobia of loud noises. As discussed above, models were specified such that the odds of a positive diagnosis could vary across individuals. Table III sum- marizes the results of these analyses. The developmental trajectories, expressed as the probability of a positive diagnosis, are shown in Figure 1. The predicted logits were converted to probabilities by:

p ¼

ð1 þ eÀlogitðpÞÞ 1

ð4Þ

The estimated slopes are not sig- nificant in any of the models, suggesting

TABLE I. Frequency and Persistence of Anxiety Diagnoses

Diagnosis	N (out of 45) with diagnosis	N meeting criteria within 5 years of initial diagnosis	Percent meeting criteria within 5 years of initial diagnosis (persistent anxiety)
Specific phobia-loud noises	27	20	74.1
Specific phobia-other	19	12	63.2
Specific phobia-blood-injury-injection	18	11	61.1
Specific phobia-animals	13	5	38.5
Specific phobia-natural environment	7	3	42.9
Generalized anxiety disorder	7	3	42.9
Social phobia	3	1	33.3
Separation anxiety	5	1	20.0

Obsessive compulsive disorder was diagnosed in only one case; none of the participants was diagnosed with panic disorder or post-traumatic stress disorder.

TABLE II. Course of Anxiety by Child

Age (in years) at first assessment

Additional anxiety

Age at most Anxiety diagnoses

Number of

diagnoses (age first

recent

Anxiety diagnoses at most at first assessment

assessments

diagnosed)

assessment

recent assessment

4 None 8 None 13 None 4 Separation anxiety 5 Social phobia (10) 10 Separation anxiety

SP-loud noises (10) Social phobia

SP-loud noises 4 SP-

loud noises 9 SP-animals (6) 13 SP-animals

SP-B-I-I (9) SP-B-I-I SP-natural environ. (11) 4 SP-animals 9 SP-loud noises (11) 13 None 4 None 6 SP-animals (8) 10 SP-animals

SP-loud noises (9) SP-loud noises 4 None 8 SP-loud noises (6) 11 None

SP-animals (9) 4 SP-animals 5 SP-B-I-I (7) 10 GAD

SP-loud noises (9) SP-animals GAD (10) 4 SP-loud noises 5 SP-natural environ. (6) 8 None

SP-animals 4 SP-loud noises 4 SP-animals (5) 7 SP-B-I-I

SP-natural environ. (6) SP-animals SP-B-I-I (6) SP-loud noises 4 SP-loud noises 3 None 8 None 4 None 3 None 7 None 4 SP-animals 4 GAD (7) 7 GAD

SP-loud noises 4 None 4 SP-animals (5) 7 SP-B-I-I

SP-loud noises (5) SP-loud noises SP-B-I-I (6) SP-animals 4 None 4 SP-animals (5) 7 None

SP-loud noises (5) 4 SP-animal 5 SP-natural environ. (7) 8 SP-animals

SP-B-I-I SP-B-I-I SP-loud noises 4 Separation anxiety 4 SP-loud noises (5) 9 SP-B-I-I

SP-B-I-I SP-natural environ. (6) SP-animals SP-animals SP-loud noises 4 None 4 SP-animals (5) 7 SP-loud noises

SP-loud noises (5) SP-animals 4 SP-loud noises 4 SP-animals (5) 7 SP-animals

SP-loud noises 4 None 3

None 6 None 4 None 3 SP-animals (5) 6 None 5 SP-B-I-I 5 GAD (10) 14 SP-animals

SP-animals SP-loud noises (10) SP-B-I-I

SP-natural environ. (11) SP-loud Noises 5 SP-animals 6 SP-B-I-I (7) 11

None

SP-loud noises (7) GAD (7)

(Continued)

that the odds of a positive diagnosis did not change with age. For the anxiety diagnosis model, the fixed effect for intercept was not significant, suggesting that the odds of a positive diagnosis (e281⁄41.32) at the median age of 9 years do not differ significantly from 1.0 for the average

TABLE II. (Continued)

Age (in years) at first assessment

Additional anxiety diagnoses (age first diagnosed)

Age at most Anxiety diagnoses

Number of

recent at first assessment

assessments

assessment

Anxiety diagnoses at most recent assessment

5 SP-B-I-I 6 None 11 None

SP-animals 5 None 8 SP-B-I-I (8) 13 None 5 None 4 None 10 None 5 None 6 SP-animals (8) 10 None

SP-loud noises (8) SP-B-I-I (9) 5 None 6 None 10 None 5 Separation anxiety 3 SP-animals (6) 10 SP-natural environ.

SP-loud noises SP-natural environ. (10) 5 SP-animals 3 None 7 None

SP-B-I-I SP-loud noises 6 None 6 SP-animals (9) 11 SP-animals

SP-loud noises (10) 6 SP-loud noises 4 SP-animals (7) 9 SP-animals

GAD (7) SP-loud noises SP-B-I-I (8) GAD 7 None 6 None 13 None 7 None 3 None 9 None 8 SP-B-I-I 8 SP-loud noises (11) 16 SP-natural environ.

SP-animal GAD (14)

SP-natural environ. (15) 8 SP-animals 4 SP-B-I-I (9) 13 SP-B-I-I 9 SP-B-I-I 6 None 16 SP-B-I-I 9 SP-B-I-I 7 SP-animals (13) 15 None 10 SP-B-I-I 3 SP-loud noises (14) 14 SP-loud noises 10 None 4 SP-natural environ. (14) 14 SP-natural environ. 10 GAD 4 SP-B-I-I (11) 13 SP-B-I-I 11 SP-natural environ. 3 SP-animals (14) 14 SP-animals 11 Separation anxiety 4 None 14 None

SP-B-I-I SP-animals 12 GAD 5 OCD (13) 16 GAD

SP-loud noises (14) SP-natural environ. SP-animals (15) 12 None 4 None 15 None 13 SP-animals 3 None 15 SP-loud noises

SP-loud noises

SP, specific phobia; B-I-I, blood-injury-injection; GAD, generalized anxiety disorder.

individual. However the test of intercept variance was significant which implies significant individual variability in the odds or predicted probability. The indi- vidual intercepts plotted as predicted probabilities are plotted as a function of each individual's age at the time he or she

entered the study. As can be seen from the figure, this individual variability is not related to differences in participants' age at the beginning of the study (Figure 2).

The results for the specific phobia diagnosis were very similar. The odds of a positive Specific Phobia diagnosis at

age 9 of 1.03 were not significantly different from 1.0. However, the average intercept was significant for the phobia for loud noises. The odds of a positive diagnosis are 0.38 which is significantly less than 1.0. The test of intercept variance is significant, indicat-

TABLE III. Multilevel Modeling Statistics for ADIS Developmental Trajectories

Fixed effects Coefficient Standard error T-ratio (df) P

Anxiety model

Intercept (log odds at

CA 1⁄49) b

0

0.28 0.29 0.95 (44) 0.348

Slope (annual change) b

1

À0.06 0.06 À0.97 (224) 0.331 Specific phobia model

Intercept (log odds at

CA 1⁄49) b

0

0.07 0.27 0.14 (44) 0.894

Slope (annual change) b

1

À0.03 0.06 À0.58 (224) 0.563 Loud noises model

Intercept (log odds at

CA 1⁄49) b

0

À0.95 0.26 À3.69 (44) 0.001

Slope (annual change) b

1

À0.05 0.07 À0.72 (224) 0.479

Random effects Standard deviation Variance $\chi 2$ (df) P

Anxiety intercept r

0

1.64 2.70 131.0 (44) <0.0001 Specific phobia intercept r

0

1.47 2.16 120.9 (44) <0.0001 Loud noises intercept r

0

1.32 1.75 105.4 (44) <0.0001

Figure 1. Predicted developmental trajectories for ADIS anxiety, specific phobia, and specific phobia of loud noises. The estimated probability of a positive diagnosis for the average individual is plotted.

ing significant variability among individ- uals in the odds of a positive diagnosis.

Relation of Anxiety to IQ and Executive Functioning

Multilevel modeling was used to test the relation between the presence of an

anxiety diagnosis and KBIT-2 Compo- site IQ. The 40 participants who had 3 or more KBIT-2 assessments were included in the analysis. The Level 1 linear model (i.e., Eq. 1) included an intercept which estimated Composite IQ at age 9 years, Composite IQ slope, and anxiety diag- nosis. The results of the model are summarized in Table IV. The average Composite IQ at age 9 years for individuals who did not have an anxiety diagnosis was 79.1. The average IQ was 1 point lower for a positive diagnosis (78.2); this difference is not statistically significant. The CA slope of À0.03 also was not significant, which suggests that average Composite IQ remained rela- tively constant over time. However, the significance tests for IQ intercept and slope variances were significant, reflect- ing individual differences in develop- mental trajectories.

Although not reported here, similar results were obtained for a model predict- ing IQ from the specific phobia diagnosis. Because the incidence of specific phobia to loud noises was relatively low, we did not relate this diagnosis to IQ.

The effect of an anxiety disorder on the developmental trajectories for the BRIEF BRI and MI T-scores was estimated in separate multilevel linear models (e.g., Eqs. 1 and 2). The

parameters estimated in the Level 1 linear model were intercept, CA slope, and presence of an anxiety disorder. This analysis was performed on the 33 participants whose parents had com- pleted the BRIEF at least three times (after the age of 6 years). The multilevel modeling results are summarized in Table V. For the BRIEF BRI the estimated intercept was 58.5, providing an estimate of the average T-score at age 9 years when the anxiety disorder diagnosis was negative. A positive anxiety disorder diagnosis resulted in a significant average increase of 3.9 points

Figure 2. Individual differences in the predicted probability of a positive ADIS anxiety diagnosis at age 9 years (i.e., intercept). The estimates are plotted as a function of the age that the individual entered the study.

TABLE IV. Multilevel Modeling Statistics for KBIT-2 Composite IQ Developmental Trajectories

Fixed effects	Coefficient	Standard error	T-ratio (df)	P
Intercept (mean at CA1⁄49) b0	79.13	2.10	36.86 (39)	<0.0001
Slope (annual change) b1	À0.03	0.44	À0.08 (39)	0.934
Anxiety (positive diagnosis)	À0.95	1.18	À0.89 (157)	0.376

Random effects	Standard deviation	Variance	χ2 (df)	P
Intercept r0	11.71	137.24	499.00 (39)	<0.0001
Slope r1	2.26	5.12	109.03 (39)	<0.0001

(62.4). The test of intercept variance was significant, indicating significant individual differences in overall level. The average slope of À0.32 was not significant, suggesting that the average BRI T-score did not change with age. Nor was the test of variability in individual slopes significant. The aver- age developmental trajectories for the predicted BRIEF BRI T-scores for positive and negative ADIS anxiety disorder diagnoses are shown in Figure 3. On average the T-scores were higher for the BRIEF MI. The average intercept was 66.7 for a negative anxiety diagnosis and 69.2 for a positive Anxiety diagnosis. This difference was not significant. However, the intercept variance was significant indicating indi- vidual variability in overall level. The average slope of À0.07 was not signifi- cant nor was the slope variance. The average developmental trajectories for the BRIEF MI T-scores are also shown in Figure 3. Models were tested relating the BRIEF BRI and MI T-scores to specific phobia diagnosis. Results were very similar and thus not reported here.

DISCUSSION

The experience of anxiety is highly prevalent in individuals with WS. Diag- nostic rates exceed those for both the GP and etiological samples with DD [e.g., Cherniske et al., 2004; Leyfer et al., 2006, 2009]. Further, anxiety is present at different ages and the symptoms appear to persist over time [Einfeld et al., 1997; Tonge and Einfeld, 2003]. However, until now little had been known about the stability of diagnoses of anxiety over time. The current study addressed three specific questions regarding diagnostic stability. First, is the course of anxiety chronic in individuals with WS? Second, what is the course for specific anxiety diagnoses? Third, is there a relation between the presence of anxiety and IQ or executive functioning?

Consistent with prior findings [e.g., Dykens, 2003; Leyfer et al., 2006, 2009], a significant proportion of the

current sample received at least one anxiety diagnosis, with a point preva- lence rate of 60% at the time of the initial assessment. The prevalence over the course of the study was 82.2%, meaning that an anxiety more than diagnosis 3

4

of the sample at received some point during the study. Unlike children who are developing typically, for whom there is a significant remission within the first year of an anxiety diagnosis [Last et al., 1996], in the current study children and adolescents with WS showed a chronic course of anxiety. The developmental trajectories showed no significant effect of age, demonstrat- ing that the presence of an anxiety