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Preschool irritability predicts child psychopathology, functional impairment, and service use at age nine

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Background: Little is known about the predictive validity and clinical significance of chronic irritability during early childhood. This prospective, longitudinal study examined associations of preschool chronic irritability with psychiatric disorders, functional impairment, and service use at age nine in a large community sample. **Methods:** Four hundred and forty-six children were assessed at age three and again at age nine. Child psychopathology and functional impairment were assessed at age three with the Preschool Age Psychiatric Assessment (PAPA) with parents and at age nine with the Kiddie-Schedule of Affective Disorders and Schizophrenia (K-SADS) with parents and children. Items from the PAPA were used to create a dimensional measure of chronic irritability at age three. At age nine, mothers, fathers, and youth completed the Child Depression Inventory (CDI) and the Screen for Anxiety Related Disorders (SCARED). **Results:** Chronic irritability at age three predicted any current and lifetime anxiety disorders at age nine, current and lifetime generalized anxiety disorder, and current separation anxiety, after controlling for baseline anxiety disorders. In addition, preschool irritability predicted increases in anxiety and disruptive behavior disorder symptoms on the K-SADS, and maternal and paternal reports of depressive and anxiety symptoms on the CDI and SCARED. Lastly, preschool irritability predicted greater functional impairment and outpatient treatment use, even after controlling for all psychiatric disorders at baseline. **Conclusions:** Findings underscore the central role of irritability in developmental psychopathology and support the importance of early detection and interventions targeting preschool irritability. **Keywords:** Preschool, irritability, longitudinal, mood dysregulation.

Introduction

Irritability, defined as low frustration tolerance characterized by anger and temper outbursts, is a common, stable, and impairing mood symptom in youth and one of the most frequent reasons for treatment referral (Brotman et al., 2006; Leibenluft, Blair, Charney, & Pine, 2003). Irritability is a criterion for several emotional and behavioral disorders, including major depressive disorder (MDD), generalized anxiety disorder (GAD), and oppositional defiant disorder (ODD), and is the cardinal feature of disruptive mood dysregulation disorder, a recent addition to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-5 (American Psychiatric Association, [APA], 2013). Despite its prevalence and central role in developmental psychopathology, irritability has been largely understudied, and surprisingly little is known about the phenomenology of irritability and its associations with psychopathology across the life span (Leibenluft & Stoddard, 2013).

A few longitudinal studies found that chronic irritability in school-aged children and adolescents predicts emotional disorders, specifically depressive and anxiety disorders, and suicidality in adulthood (Brotman et al., 2006; Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006; Stringaris, Cohen, Pine, & Leibenluft, 2009). Youth irritability has also been associated with significant functional impairment even in the absence of psychiatric disorders (Stringaris & Goodman, 2009b) and predicted lower income and less educational attainment in a 20-year follow-up study (Stringaris et al., 2009). In addition to its associations with internalizing disorders, irritability has been related to externalizing behavior problems in youth (Brotman et al., 2006; Leibenluft et al., 2006; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012; Stringaris et al., 2009), which may explain the comorbidity between internalizing and externalizing disorders and the developmental link between ODD in youth and depression in adulthood (Stringaris, Maughan, & Goodman, 2010).

We previously provided the first data supporting the predictive validity of chronic irritability in children as young as age 3 years on children's emerging psychopathology and impairment using data from the Stony Brook Temperament Study, a large community-based longitudinal study (Dougherty et al., 2013). Consistent with findings in older youth, we found that chronic irritability at age three predicted depression, ODD, and poorer functional impairment at age six, over and above baseline psychopathology. Although irritability is relatively common in early childhood, these findings provide compelling

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evidence that more frequent irritability in early childhood holds clinical utility in identifying high-risk children. Moreover, studying the developmental course and predictive validity of early chronic irritability will help determine whether the pattern of irritability-psychopathology associations is similar to studies of older youths and adults. Lastly, investigating irritability at this young stage of development may prove beneficial for early identification and lead to more effective interventions that can significantly alter the trajectory of impairing irritability.

In this article, we aim to extend our findings by testing the longitudinal associations between preschool irritability and clinical outcomes at age nine. Our primary aim was to examine whether chronic irritability assessed at age three predicts psychiatric disorders and symptoms, functional impairment, and service use at age nine in unadjusted models and in models adjusting for baseline disorders and symptoms. Based on prior work in older youth demonstrating that chronic irritability shows strong associations with both emotional and behavioral disorders (Brotman et al., 2006; Leibenluft et al., 2006; Stringaris & Goodman, 2009a,c; Stringaris et al., 2009, 2012), we hypothesized that preschool chronic irritability would prospectively predict depression, anxiety, and disruptive behavior disorders (DBD) at age nine. We also hypothesized that preschool irritability would predict greater functional impairment and service use at age nine, even after accounting for psychiatric disorders at baseline. As an exploratory analysis, we examined whether associations between preschool irritability and youth clinical outcomes at age nine differed by gender.

Methods

Participants

The Stony Brook Temperament Study is a longitudinal study investigating the role of early temperament on the development of psychiatric disorders (Dougherty et al., 2011). We recruited families with a 3-year-old child living within 20 contiguous miles of Stony Brook University. Potential participants were identified via a commercial mailing list; eligible families had a child between 3 and 4 years of age with no significant medical conditions or developmental disabilities, and at least one English-speaking biological parent. Of the 815 families who were identified as eligible, 66.4% ($N = 541$) entered the study and provided diagnostic information about the child. There were no significant differences between families who did and did not participate on demographic variables. Table 1 presents demographic and sample characteristics. Census data suggest that the sample is reasonably representative of the surrounding county. The study was approved by the human subjects review committee. Informed consent was obtained from parents, and child assent was obtained at age nine; families were compensated for participating.

Parents were interviewed regarding their 3-year-old child ($M = 3.5$ years, $SD = 0.3$). Of the 541 families, 446 (82.4%) participated in the age nine follow-up assessment ($M = 9.3$ years, $SD = 0.4$): 446 completed questionnaires about the child's current depressive and anxiety symptoms; 443 primary caregivers and the child completed a diagnostic clinical interview at the age nine assessment. Children who completed both the age three and nine assessments were compared to children who completed only the first assessment on age three demographic variables, irritability, and diagnoses/symptoms. No significant differences were observed.

Measures

Age three assessment. Preschool age psychiatric disorders: Parents (98.0% mothers) were interviewed using the Preschool Age Psychiatric Assessment (PAPA; Egger et al., 2006), a structured diagnostic interview designed to assess a range of DSM-IV psychiatric disorders in preschoolers. As described elsewhere (Bufferd, Dougherty, Carlson, & Klein, 2011), DSM-IV diagnoses were derived using algorithms created by the instrument's developers. Disorders included any depressive disorder [MDD, dysthymic disorder, depressive disorder-not otherwise specified (NOS)]; any anxiety disorder (specific phobia, separation anxiety disorder, social phobia, GAD, agoraphobia, selective mutism); attention-deficit/hyperactivity disorder (ADHD), and ODD. Symptoms occurring 3 months prior to the interview were rated to maximize recall. For information on the interview's psychometric properties, see Egger et al. (2006).

Interviews were conducted by four advanced graduate students in clinical psychology who received training from an experienced interviewer from the developer's group. Interviews usually lasted 2 hr and were conducted by telephone. Diagnostic interviews with parents regarding their children have yielded equivalent results when administered by telephone and face-to-face (Lyneham & Rapee, 2005). Based on 21 randomly selected audiotaped interviews that over-sampled participants with psychopathology, kappas were 1.00 for all diagnostic categories.

Preschool irritability: For a complete description of the preschool irritability scale, see Dougherty et al. (2013). Six items from the PAPA were used to assess irritability: (a) irritable mood (depression section), (b) feelings of anger/bad temper under minor provocation (depression section), (c) displays of anger under minor provocation (depression section), (d) feelings of frustration under minor provocation (depression section), (e) discrete episodes of temper without violence (ODD section), and (f) discrete episodes of excessive temper, manifested by shouting, crying, or stamping, and/or involving violence/damage (ODD section).

Preschool Age Psychiatric Assessment items were rated for intensity, frequency, and duration. The intensity rating indicates whether a symptom was absent or present and the extent to which it was intrusive, interfering, and generalizable across activities. A rating of two or higher on a two or three-point scale indicates that the symptom was present at a threshold level of intensity. Frequency items reflect the number of occurrences during the last 3 months. Following Brotman et al.'s (2006) and Copeland, Angold, Costello, and Egger's (2013) guidelines for chronic irritability, items were coded as present if a child engaged in the behavior at least 45 times in the past 3 months. To assess whether the irritable mood state persisted for a clinically significant period of time, the duration criterion was coded as present if the child was rated as having at least a 30-min duration on irritable mood, prone to frustration, annoyance or anger, or difficulty recovering from temper tantrums. The total irritability scale consisted of the sum of symptoms coded as present according to the intensity, frequency, and

Table 1 Demographic and clinical characteristics of the study sample

	Age 3	Age 9	
Demographic characteristics			
Child mean age: years (*SD*)	3.51 (.26)	9.25 (.42)	
Child gender: female *n* (%)	207 (46.4)		
Child race: *n* (%)			
White	421 (94.4)		
Black/African-American	13 (2.9)		
Asian	11 (2.5)		
Other	1 (.2)		
Child Hispanic/non-Hispanic ethnicity: *n* (%)	39 (8.7)		
Biological parents' marital status: *n* (%)			
Married	416 (93.3)		
Divorced, separated, or widowed	12 (2.7)		
Never married	17 (3.8)		
Parents' education: graduated college *n* (%)			
Mother	249 (55.8)		
Father	204 (45.7)		0–7
Mean child irritability at age 3 (0–7) (*SD*; range)	.72 (1.31)		
Child psychopathology *n* (%)			
Current Depressive Disorder	6 (1.3)	3 (.7)	
Lifetime Depressive Disorder		9 (2.0)	
Current Anxiety Disorder	88 (19.7)	86 (19.4)	
Lifetime Anxiety Disorder		103 (23.5)	
Current Specific Phobia	41 (9.2)	41 (9.3)	
Lifetime Specific Phobia		49 (11.0)	
Current Social Phobia	18 (4.0)	16 (3.6)	
Lifetime Social Phobia		17 (3.8)	
Current Separation Anxiety	26 (5.8)	15 (3.4)	
Lifetime Separation Anxiety		26 (5.9)	
Current GAD	19 (4.3)	20 (4.5)	
Lifetime GAD		21 (4.7)	
Current ADHD	9 (2.0)	58 (13.1)	
Lifetime ADHD		58 (13.1)	
Current ODD	46 (10.3)	11 (2.5)	
Lifetime ODD		13 (2.9)	
Current DBD		15 (3.4)	
Lifetime DBD		18 (4.1)	
Mean child symptom scales at age 9 (*SD*; range)			
Maternal-reported CDI		7.25 (4.95)	0–29
Paternal-reported CDI		7.42 (4.46)	0–23
Child-reported CDI		4.77 (4.17)	0–22
Maternal-reported SCARED		7.97 (8.01)	0–55
Paternal-reported SCARED		6.81 (6.65)	0–36
Child-reported SCARED		19.16 (10.92)	1–53
Child functioning at age 9			
Child mean CGAS (*SD*; range)		78.73 (11.02)	45–99
Child mean impairment ratings (*SD*; range)		2.31 (.39)	1.50–4.13
Outpatient treatment services (%)		85 (19.2)	
Psychotropic medication use (%)		34 (7.7)	
Child mean age at first treatment: years (*SD*; range)		6.46 (1.85)	1–10

N = 446; 443 children completed the K-SADS only. *SD*, standard deviation; GAD, generalized anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; DBD, disruptive behavior disorder; CDI, Child Depression Inventory; SCARED, Screen for Child Anxiety Related Disorders; CGAS, Children's Global Assessment Scale.

duration criteria described above. Internal consistency (Cronbach α) was .73.

Given that individual PAPA items used to derive the irritability scale were also used to derive diagnoses for any depressive disorder, any anxiety disorder, and ODD, we created 'nonoverlapping' age three symptom scales for each diagnostic category to avoid item overlap in analyses controlling for age three symptoms. Symptom scales were created by summing items in each diagnostic category, excluding any irritability items. No adjustment was needed for ADHD. Interrater reliability [intraclass correlation coefficient (ICC)] and internal consistency (α) for the nonoverlapping symptom scales ranged from .97–.99. and .53–.89, respectively.

Age nine assessment. Child psychiatric disorders: One parent (92.2% mothers) and the child were interviewed using the Kiddie-Schedule of Affective Disorders and Schizophrenia–Present and Lifetime (K-SADS-PL; Axelson, Birmaher, Zelazny, Kaufman, & Gill, 2009). Doctoral students in clinical psychology and a master's-level clinician administered the K-SADS first to the parent and then to the child. Further information was obtained to reconcile discrepancies. Summary ratings for each symptom were derived based on the combination of parent and child reports. Administration of the K-SADS was supervised in a group format by an experienced child psychiatrist and licensed clinical psychologist. Current and

lifetime diagnoses were derived for the following DSM-IV-TR psychiatric disorders: any depressive disorder (MDD, dysthymic disorder, depressive disorder-NOS); any anxiety disorder (specific phobia, social phobia, separation anxiety, GAD, panic, agoraphobia, obsessive compulsive, post-traumatic stress, acute stress, anxiety disorder-NOS); any DBD (ODD, conduct disorder, DBD-NOS); and any ADHD (ADHD-inattentive, hyperactivity or combined type, ADHD-NOS). Current symptoms of any depression (α = .84), anxiety (α = .85), DBD (α = .73), and ADHD (α = .86) were rated on a 3-point scale (0 = not present; 1 = subthreshold; 2 = threshold) and were summed to create dimensional scores. To assess interrater reliability, a second rater independently derived ratings from videotapes for 74 participants. Kappas for lifetime diagnoses ranged from .58 to .85. Intraclass correlations for dimensional scores ranged from .77 to .97.

Child depressive and anxiety symptoms: At age nine, 440 mothers (α = .79), 395 fathers (α = .76), and 436 children (α = .74) completed the 27-item Child Depression Inventory (CDI; Kovacs, 1992), and 440 mothers (α = .90), 396 fathers (α = .88), and 436 children (α = .73) completed the 41-item Screen for Child Anxiety Related Disorders (SCARED; Birmaher et al., 1999) to assess children's current depressive and anxiety symptoms respectively. Informant reports were significantly correlated. Correlations between maternal and paternal-reported CDI and SCARED scores were .46 and .59 respectively. Correlations ranged from .14 to .21 between either maternal or paternal and youth reports.

Functional impairment: The K-SADS interviewer completed the Children's Global Assessment Scale (CGAS) and functional impairment ratings following the administration of the K-SADS. The CGAS is a global measure of children's level of functioning (Shaffer et al., 1983). Scores range from 0 to 100, where 0 indicates the worst functioning and 100 indicates superior functioning. Impairment was also rated across several domains (parental relationship quality, household and recreational activities, sibling relationships, peer relationships, school life, overall satisfaction) on a 5-point scale ranging from 0 (very good functioning/no impairment) to 4 (very poor functioning/severe impairment) and averaged across domains for a mean total impairment rating. The interrater reliability (ICC) for the CGAS and mean impairment ratings was .56 and .77 respectively.

Service use: The K-SADS interviewer assessed whether the child ever received psychotherapy or was prescribed psychotropic medication for a mental health problem, and the age at which treatment was first sought.

Data analyses

Binary logistic regression analyses were conducted to examine longitudinal associations between irritability at age three and current and lifetime psychiatric diagnoses at age nine (depressive disorder, anxiety disorder, DBD, and ADHD). Odds ratios (OR) provide the effect size estimate. Separate models were run for each of the four diagnoses. Given longitudinal associations between irritability and specific anxiety disorders, particularly GAD (Stringaris et al., 2009), we also examined associations between preschool irritability and age nine specific phobia, social phobia, separation anxiety, and GAD. The irritability measure was standardized (z-score) and entered as the independent variable. Models included child's current age, gender, and parental education as covariates if they were significantly associated with the outcome variable. Models predicting diagnostic outcomes at age nine were adjusted for the corresponding baseline disorder at age three. Linear regression analyses were used to examine longitudinal associations between preschool irritability and symptoms scales at age nine. We report unadjusted models and models adjusted for the corresponding age three nonoverlapping symptom scale.

Linear regression analyses were used to examine longitudinal associations between preschool irritability and functional impairment ratings at age nine and children's age at first treatment initiation. Models examining associations with children's age at first treatment initiation were limited to children who sought treatment (n = 85). Logistic regression analyses were used to examine longitudinal associations between preschool irritability and outpatient treatment and psychotropic medication use. We report unadjusted models and models adjusted for all age three psychiatric disorders (any depressive disorder, any anxiety disorder, ODD, and ADHD). Lastly, all logistic and linear regression analyses were rerun with preschool irritability, gender, and an irritability X gender interaction term entered as independent variables to explore whether gender moderated associations between preschool irritability and age nine outcomes.

Results

Child gender and age and parental education were examined as potential covariates. Boys were more likely to meet criteria for current and lifetime ADHD and DBD, had greater maternal, paternal, and youth-reported CDI scores, higher impairment ratings, and lower CGAS scores at age nine than girls. If neither parent had a four-year college degree, children were more likely to meet criteria for current and lifetime social phobia, had greater maternal-rated CDI and SCARED scores, higher impairment ratings, and lower CGAS scores at age nine than children with at least one parent with a four-year college degree. These analyses are presented in Table S1, available online. No associations were observed for child age.

Preschool irritability as predictor of psychiatric disorders at age nine

Table 2 shows associations between irritability at age three and current and lifetime disorders at age nine, unadjusted and adjusted for the corresponding age three disorder. In unadjusted models, irritability at age three significantly predicted current and lifetime any anxiety disorder, specific phobia, separation anxiety, GAD, ADHD, and DBD at age nine. After controlling for the corresponding baseline disorder, preschool irritability remained a significant predictor of current and lifetime any anxiety disorder, current and lifetime GAD, and current separation anxiety disorder.[1]

Preschool irritability as predictor of psychiatric symptoms at age nine

Table 3 shows associations between irritability at age three and children's current psychiatric symptoms at age nine, unadjusted and adjusted for the corresponding age three symptom scale. In unadjusted models, irritability at age three significantly

Table 2 Irritability at age 3 as predictor of DSM-IV disorders at age 9

	Age 3 irritability			
	Not adjusted		Adjustment for corresponding age 3 disorder	
Disorder at age 9	Odds ratio	95%CI	Odds ratio	95%CI
Current Depressive Disorder	.00	.00–.00	.00	.00–.00
Lifetime Depressive Disorder	1.27	.75–2.16	1.06	.56–1.99
Current Anxiety Disorder	1.31*	1.07–1.62	1.27*	1.03–1.58
Lifetime Anxiety Disorder	1.31**	1.07–1.60	1.24*	1.00–1.52
Current Specific Phobia	1.33*	1.02–1.73	1.30†	.99–1.69
Lifetime Specific Phobia	1.30*	1.02–1.67	1.24	.96–1.60
Current Social Phobia	.97	.58–1.61	.96	.57–1.62
Lifetime Social Phobia	.93	.55–1.55	.92	.54–1.56
Current Separation Anxiety	1.54*	1.07–2.23	1.50*	1.01–2.20
Lifetime Separation Anxiety	1.53**	1.14–2.05	1.37†	1.00–1.88
Current GAD	1.77***	1.30–2.42	1.68**	1.20–2.35
Lifetime GAD	1.72**	1.26–2.33	1.63**	1.17–2.27
Current ADHD	1.28*	1.01–1.63	1.26†	.99–1.61
Lifetime ADHD	1.28*	1.01–1.63	1.26†	.99–1.61
Current DBD	1.60*	1.11–2.31	1.35	.81–2.25
Lifetime DBD	1.88***	1.35–2.61	1.44	.90–2.29

†$p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$.
CI, Confidence Interval; GAD, generalized anxiety disorder; ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behavior disorder.

Table 3 Irritability at age three as predictor of symptom scores at age 9

	Age three irritability			
	Not adjusted		Adjustment for corresponding age 3 scale	
Symptoms at age 9	ß	B (*SE*)	ß	B (*SE*)
Depressive symptom scale	.01	.02 (.08)	−.03	−.05 (.09)
Anxiety symptom scale	.21***	1.17 (.26)	.14**	.76 (.26)
ADHD symptom scale	.12**	.21 (.08)	.01	.02 (.08)
DBD symptom scale	.41***	1.04 (.11)	.22***	.55 (.13)
Maternal-reported CDI	.23***	1.14 (.23)	.17**	.81 (.24)
Paternal-reported CDI	.19***	.83 (.22)	.15**	.68 (.23)
Child-reported CDI	.06	.23 (.20)	.04	.16 (.21)
Maternal-reported SCARED	.21***	1.65 (.37)	.12*	.95 (.37)
Paternal-reported SCARED	.17**	1.14 (.33)	.11*	.71 (.33)
Child-reported SCARED	.001	.01 (.52)	−.03	−.28 (.54)

*$p < .05$, **$p < .01$, ***$p < .001$.
ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behavior disorders; CDI, Child Depression Inventory; SCARED, Screen for Child Anxiety Related Disorders.

predicted K-SADS current anxiety, ADHD, and DBD symptom scale scores, and maternal and paternal-reported CDI and SCARED total scores at age nine. All associations remained significant in adjusted models, with the exception of ADHD symptoms.

Preschool irritability as predictor of functional impairment and service use at age nine

Irritability at age three significantly predicted lower CGAS scores and higher mean ratings of impairment at age nine (Table 4). These associations remained significant after controlling for any depressive disorder, anxiety disorder, ADHD, and ODD at age three. In addition, preschool irritability significantly predicted outpatient treatment use and a younger age at first treatment initiation. Preschool irritability remained a significant predictor of outpatient service use after controlling for all baseline psychiatric disorders.

Potential gender differences

In adjusted models controlling for the corresponding baseline disorder, there were significant interactions between preschool irritability and child gender in predicting lifetime anxiety disorder (OR = .58, CI = .37–.91, $p = .02$) and current (OR = 1.91, CI = 1.15–3.19, $p = .01$) and lifetime ADHD (OR = 1.91, CI = 1.15–3.19, $p = .01$) at age nine.

Table 4 Irritability at age three as predictor of functional impairment and service use at age 9

	Age three irritability			
	Not adjusted		Adjustment for all disorders at age 3	
Functional impairment at age 9	ß	B (*SE*)	ß	B (*SE*)
CGAS	−.20***	−2.17 (.51)	−.16*	−1.71(.66)
Mean impairment ratings	.21***	.08 (.02)	.15*	.06(.02)
Age at first treatment	−.25*	−.34 (.15)	−.15	−.20(.21)
	OR	95%CI	OR	95%CI
Outpatient service	1.51***	1.23–1.85	1.32*	1.00–1.74
Psychotropic medication	1.30†	.97–1.73	1.18	.79–1.77

†$p < .10$, *$p < .05$, **$p < .01$, ***$p < .001$.
CGAS, Children's Global Assessment Scale; OR, Odds Ratio; CI, Confidence Interval; *SE*, Standard Error.

Preschool irritability predicted lifetime anxiety disorder at age nine for girls (OR = 1.54, CI = 1.18–2.02, $p = .002$) but not boys (OR = .89, CI = .62–1.28, $p = .54$). In contrast, preschool irritability predicted current and lifetime ADHD at age nine for boys (OR = 1.99, CI = 1.31–3.01, $p = .001$) but not girls (OR = 1.04, CI = .77–1.40, $p = .80$). Given that children with current or lifetime ADHD were the same subgroup of 58 children, results were identical for current and lifetime ADHD.

Discussion

Using data from a large, community-based sample of preschoolers, we previously reported that chronic irritability at age three predicted depression, ODD, and poorer functional impairment at age six, over and above baseline psychopathology. For this report, we examined the longitudinal associations between symptoms of chronic irritability at age three and clinical outcomes at age nine. We found that chronic irritability at age three predicted any current and lifetime anxiety disorder, current and lifetime GAD, and current separation anxiety, after controlling for baseline anxiety disorders. In addition, preschool irritability predicted increases in anxiety and DBD symptoms on the K-SADS, and maternal and paternal reports of depressive and anxiety symptoms on the CDI and SCARED. Lastly, preschool irritability predicted greater functional impairment and outpatient treatment use, even after controlling for psychiatric disorders at baseline.

In contrast with associations observed at age six, preschool irritability showed the most consistent predictive associations with anxiety disorders at age nine, including GAD and separation anxiety, and predicted increases in anxiety symptoms from age three to age nine. These findings are consistent with long-term follow-up studies of irritability in older youth demonstrating that irritability predicts anxiety disorders, particularly GAD, in adulthood (Brotman et al., 2006; Stringaris et al., 2009). The association between preschool irritability and childhood GAD is particularly noteworthy given that childhood GAD predicts the poorest adult outcomes across all functional domains (Copeland, Angold, Shanahan, & Costello, 2014) and accounts for the longitudinal association between childhood anxiety and adult depression (Copeland, Shanahan, Costello, & Angold, 2009). Taken together, these findings suggest that irritability may lead to adult anxiety and depressive disorders via a pathway that involves childhood anxiety disorders, and GAD in particular may explain longitudinal associations between youth irritability and adult depression and functional impairment.

While preschool irritability did not predict current or lifetime depressive disorders or current symptoms based on the K-SADS, it did predict increases in maternal- and paternal-reported depressive symptoms on the CDI. The association between preschool irritability and increases in depressive symptoms at age nine is consistent with evidence linking youth irritability to subsequent depressive disorders (Brotman et al., 2006; Stringaris et al., 2009) and findings supporting their shared genetic influences (Stringaris et al., 2012). While current (0.7%) and lifetime (2.0%) depressive disorders were rare at age nine based on the K-SADS, the CDI is more sensitive to variations in youths' depressive symptoms at the lower end of the continuum (Olino et al., 2012). Furthermore, depressive symptoms in middle childhood are moderately stable and hold clinical significance in predicting later onset of depressive disorders and functional impairment (Keenan et al., 2008).

Preschool irritability also predicted current and lifetime DBD and ADHD disorders and symptoms. However, in adjusted models controlling for the corresponding baseline diagnosis or symptoms, only the association between preschool irritability and DBD symptoms at age 9 remained. Studies of older youth have also reported that irritability is concurrently (Stringaris et al., 2009) and longitudi-

nally (Leibenluft et al., 2006) associated with both emotional and behavioral disorders in adolescence. Our finding that preschool irritability predicted increases in DBD symptoms is noteworthy as externalizing problems, specifically ODD, predict depression in adulthood over and above depression in childhood (Copeland et al., 2009). Thus, irritability predicts both externalizing and internalizing problems and likely plays a role in longitudinal associations between externalizing problems and depression (Stringaris & Goodman, 2009a,c). These findings also suggest that irritability is a risk factor shared by both internalizing and externalizing symptoms in early childhood, perhaps increasing risk for each as well as their co-occurrence. Irritability may be an important phenotype that crosses diagnostic categories and may help identify unique and overlapping mechanisms in youth psychopathology.

Chronic irritability by age 3 years predicted impairment across multiple functional domains, mental health service use, and younger age at the first initiation of treatment. Associations between preschool irritability and later functional impairment and service use persisted even after controlling for preschool psychiatric disorders. These findings strongly argue for the early identification of chronic irritability in young children and the importance of intervening as early as possible. Furthermore, to develop effective interventions for this high-risk group, we need to identify the processes and mechanisms by which irritability in young children lead to impairment and treatment referral. Irritable youth likely have a wide range of deficits in social, emotional, and cognitive-control processes, and in underlying neurodevelopmental brain circuitry that contribute to functional impairment. Thus, identifying the multiple determinants involved in the etiology and maintenance of irritability will help determine treatment targets.

While previous studies have controlled for gender, no previous study, to our knowledge, has examined gender differences in associations between youth irritability and clinical outcomes. Gender differences are not typically found in youth irritability but they are frequently observed in psychiatric symptoms and disorders across the life span (Dougherty et al., 2013; Stringaris et al., 2009). In our exploratory analyses controlling for the corresponding baseline disorder, we found that preschool irritability predicted lifetime any anxiety disorder at age nine only for girls, and preschool irritability predicted current and lifetime any ADHD at age nine only for boys. We did not observe gender differences for other diagnoses or for symptom scales, impairment, or service use. Given that these associations were specific to diagnoses, they should be interpreted with caution as statistical power and sample size decrease when diagnoses are subdivided by gender. Nevertheless, these findings provide important information: irritability may play a different role in pathways to psychopathology for girls and boys. This is particularly important given the gender differences that emerge for anxiety in adolescence and the preponderance of boys with ADHD. It will be important for future research to continue examining gender differences in the developmental trajectories from childhood irritability to later psychopathology.

This study had several strengths. First, we assessed child psychopathology and irritability using a comprehensive interview, which allowed us to take into account the intensity, frequency, and duration of irritability. Second, we used a dimensional construct of youth irritability, as the boundaries between clinically significant irritability and normative irritability, particularly in preschoolers, continue to be investigated (Wakschlag et al., 2012). This approach is consistent with the NIMH Research Domain Criteria project, which aims to identify new ways to classify behavior based on dimensional measures of behavior and neurobiological processes (Insel et al., 2010). Third, we used a community sample of preschoolers, which is important as irritability is common in the course of typical development.

The study also had several limitations. First, assessments of irritability and psychiatric diagnoses were both largely based on parent-report; however, our findings do not seem to be due to shared method variance because psychopathology at age nine was assessed by interviewing both the parent and child and because we found meaningful associations between irritability and both maternal- and paternal-reported symptoms. Nevertheless, it is important to note that our findings demonstrated discrepancies when the informant was the youth. It appears that child and parent report are capturing different aspects of the youth's emotional experience, as has been shown elsewhere (Mesman & Koot, 2000; Stringaris et al., 2009). Second, the PAPA interviews were conducted by telephone, rather than face-to-face, with the parent and did not evaluate the child directly. Third, there is currently no validated measure of chronic irritability for preschoolers; we derived a measure of chronic irritability based on responses in a diagnostic interview. Lastly, the sample was largely white and middle class. Future research should extend this research to more diverse samples.

In summary, our findings underscore the clinical significance of irritability in early childhood. Preschool irritability predicted anxiety disorders, increases in anxiety, depressive and DBD symptoms, functional impairment, and service use 6 years later even after controlling for baseline psychopathology. Further work on irritability in preschoolers may help us refine how we classify and treat preschool mental health problems. Specifically, more longitudinal work is needed to delineate the processes through which preschool irritability develops into adolescent and adult phenotypes. Finally, future research needs to examine the mechanisms involved in early chronic irritability, including genetic and environmental

influences, as well as associated affective and cognitive processes and neural circuitry.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Youth clinical outcome characteristics at age 9 by gender and parental education.

Table S2. Internal consistency statistics for study measures.

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Key points

- A few prospective studies have shown that youth irritability predicted emotional disorders, suicidality, functional impairment, and lower educational attainment and income in adulthood. However, little is known about the clinical significance of chronic irritability during early childhood.
- Preschool irritability predicted anxiety disorders, increases in anxiety, depressive and disruptive behavior disorder symptoms, functional impairment and service use 6 years later even after controlling for baseline psychopathology.
- These findings argue for the early identification of chronic irritability in young children and the importance of intervening as early as possible.
- Further research is needed to delineate the processes through which preschool irritability leads to later psychopathology and impairment with the goal of identifying targets for early intervention.

Note

1. We ran an additional model in which we regressed age nine diagnoses (any depression, anxiety, ADHD, and DBD) on age three irritability to determine which disorder(s) is uniquely associated with early irritability. We found that age three irritability was uniquely associated with age nine current anxiety ($b = .33$, $SE = .12$, $p = .007$) and DBD ($b = .68$, $SE = .28$, $p = .014$) diagnoses and not current depressive ($b = -.84$, $SE = .58$, $p = .15$) and ADHD ($b = .18$, $SE = .15$, $p = .24$) diagnoses. Similar findings were observed for lifetime diagnoses at age nine.

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