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The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis

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Background: Recent studies have identified a Child Behavior Checklist profile that characterizes children with severe affective and behavioral dysregulation (CBCL-dysregulation profile, CBCL-DP). In two recent longitudinal studies the CBCL-DP in childhood was associated with heightened rates of comorbid psychiatric disorders, among them bipolar disorder, an increased risk for suicidality, and marked psychosocial impairment at young-adult follow-up. This is the first study outside the US that examines the longitudinal course of the CBCL-DP. **Methods:** We studied the diagnostic and functional trajectories and the predictive utility of the CBCL-DP in the Mannheim Study of Children at Risk, an epidemiological cohort study on the outcome of early risk factors from birth into adulthood. A total of 325 young adults (151 males, 174 females) participated in the 19-year assessment. **Results:** Young adults with a higher CBCL-DP score in childhood were at increased risk for substance use disorders, suicidality and poorer overall functioning at age 19, even after adjustment for parental education, family income, impairment and psychiatric disorders at baseline. Childhood dysregulation was not related to bipolar disorder in young adulthood. The CBCL-DP was neither a precursor of a specific pattern of comorbidity nor of comorbidity in general. **Conclusions:** Children with high CBCL-DP values are at risk for later severe, psychiatric symptomatology. The different developmental trajectories suggest that the CBCL-DP is not simply an early manifestation of a single disease process but might rather be an early developmental risk marker of a persisting deficit of self-regulation of affect and behavior. **Keywords:** Dysregulation, childhood, comorbidity, longitudinal, irritability, depression, ADHD, substance use, suicidality, CBCL, bipolar. **Abbreviations:** CBCL-DP: Child Behavior Checklist-dysregulation profile; SMD: severe mood dysregulation; BD: bipolar disorder.

Severe affective and behavioral dysregulation, including irritability, aggression, 'affective storms', hyperarousal and mood instability, presents a clinically challenging phenotype in a sizable number of youth. Nevertheless, youth presenting with this dysregulation complex do not fit neatly into any current diagnostic category (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003), and therefore have been called 'nosologic orphans' (Carlson, 1998).

The Child Behavior Checklist (Achenbach, 1991) is one of the best-studied, empirically derived parent checklists to measure general child and adolescent psychopathology. Recently, a profile has been identified on this measure that captures the mixed phenotype of severe dysregulation (CBCL-dysregulation profile, CBCL-DP; Althoff, 2010). This profile is characterized by simultaneous extreme values on the syndrome scales Anxious/Depressed, Attention Problems, and Aggressive Behavior. The CBCL-DP has been consistently found to be associated with disruptive behavior disorders, suicidal behavior, and reduced need for sleep (Ayer et al., 2009; Meyer et al., 2009; Holtmann et al., 2007, 2008; Hudziak et al., 2005; Volk & Todd, 2007).

Two possible models have been suggested for how severe dysregulation and the diagnostic value of the CBCL-DP may actually be conceptualized. Severe dysregulation may (1) constitute a syndrome unto itself (Klein & Riso, 1993). In other words, it has been suggested that children with CBCL-DP may suffer from a single disorder rather than three coexisting disorders (Hudziak et al., 2005). Previous studies revealed evidence of high heritability (Hudziak et al., 2005; Boomsma et al., 2006), longitudinal stability (Boomsma et al., 2006), and neurometabolic (Zepf, Wöckel, Poustka, & Holtmann, 2008) and endocrine

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(Holtmann, Duketis, Goth, Poustka, & Bölte, 2010a) correlates of the CBCL-DP. However, the evidence to support the conceptualization of the CBCL-DP as a single syndrome is not sufficient (Ayer et al., 2009). Indeed, some have suggested (2) that the CBCL-DP is not a measure of any particular syndrome or of a circumscribed nosological entity, but instead of complex comorbidity (Carlson, Bromet, & Sievers, 2000). Over the past few decades, a number of seminal papers have underscored the importance of taking comorbidity into account for understanding the etiology, course and treatment of psychiatric disorders (e.g., Caron & Rutter, 1991; Klein & Riso, 1993; Angold, Costello, & Erkanli, 1999). Given that the CBCL-DP consists of the simultaneous elevation of three preexisting CBCL scales, severe dysregulation could indicate comorbid internalizing and externalizing problems, such as co-occurring ADHD or oppositional defiant disorder and depression. In a recent cross-sectional community study, mood lability, a concept closely linked to dysregulation, has been shown to be strongly associated with comorbidity between internalizing and externalizing disorders, suggesting that it could be a shared risk factor for both disorders (Stringaris & Goodman, 2009).

Caron and Rutter (1991) have suggested some general guidelines for testing alternative hypotheses applying to coexisting psychopathology. Their nosological considerations provide a valuable framework to examine the nature and course of severe dysregulation. With regard to childhood dysregulation, two of their proposed models are of special interest: severe dysregulation as captured by the CBCL-DP could represent an early manifestation of a yet unidentified category whose manifestation changes with age: in general, the term heterotypic continuity has been used to refer to processes of this kind. A further possibility is that dysregulation is a dimension of risk underlying later psychopathology. To shed light on this issue it is crucial to examine the development of severe dysregulation across time.

Recently, two longitudinal studies have followed children with the CBCL-DP to young adulthood (Meyer et al., 2009; Biederman et al., 2009). In a longitudinal study of youth at high risk for mood disorders, Meyer et al. (2009) found that CBCL-DP in childhood was associated with marked psychosocial impairment, increased rates of suicidal thoughts and behaviors, and heightened risk for anxiety disorder, bipolar disorder, cluster B personality disorder and ADHD in young adulthood. In a sample of ADHD children followed-up to late adolescence, Biederman et al. (2009) observed that a CBCL-DP score (the unweighted sum of the three CBCL-DP subscales) above 180 (i.e., 1 SD above average) at baseline predicted impaired psychosocial functioning, a higher risk for psychiatric hospitalization, and diagnoses of conduct disorder, depression and bipolar disorder at follow-up. This led to the conclusion that dysregulation in childhood may be best interpreted as a predictor of overall psychopathology, impairment and self-regulation problems, rather than any particular diagnosis proposed by the current classificatory systems (Ayer et al., 2009; Meyer et al., 2009; Diler et al., 2009). This view is supported by the finding that dysregulation of affect and behavior may be an early-appearing temperamental trait predicting future maladjustment (Eisenberg et al., 2009) and psychiatric disorders (Caspi, 2000). Likewise, Lahey et al. (2008) have provided evidence that childhood dispositions to respond emotionally to the environment are posited to be key factors in the development of later psychopathology.

In the present study, we used the CBCL-DP as a heuristic tool to examine the diagnostic and functional trajectories of severe childhood dysregulation in a German epidemiological cohort enriched with children born at risk for later psychopathology who were followed at regular intervals from birth into adulthood. This is the first study outside the US that examines the longitudinal course of the CBCL-DP. Based on the findings of the two previous longitudinal studies (Meyer et al., 2009; Biederman et al., 2009), we expected that the CBCL-DP would represent a dimension of risk that sets the stage for a broader range of adult psychopathology. Specifically, we hypothesized that participants with high CBCL-DP scores in childhood would exhibit heightened rates of internalizing and externalizing disorders, an increased risk for substance use, suicidal ideation and behavior, and psychosocial impairment at young-adult follow-up. Given the weak association between the CBCL-DP and bipolar disorder in cross-sectional studies (Diler et al., 2009; Holtmann et al., 2008), we did not expect to find elevated rates of bipolarity following high CBCL-DP scores in childhood.

Materials and methods

Sample. The participants in the Mannheim Study of Children at Risk, an epidemiological cohort study on the outcome of early risk factors from birth into adulthood, were utilized for the present investigation. The initial sample consisted of 384 children of predominantly (>99.0%) European descent born between 1986 and 1988. Infants were recruited from two obstetric and six children's hospitals of the Rhine-Neckar Region of Germany and were included consecutively into the sample according to a two-factorial design intended to enrich and control the risk status of the sample (factor 1 varying the degree of biological risks, and factor 2 the degree of psychosocial risks). Biological risk was defined by the degree of obstetric complications, such as preterm birth, gestosis of the mother, neonatal seizures or sepsis. Psychosocial risk was derived from a family risk index measuring the presence of 11 adverse family factors covering characteristics of the parents (e.g., low education), the partnership (e.g., discord), and the family environment (e.g., overcrowding) during a period of 1 year prior to birth (for full details see supplementary material; details of the sampling procedure

have been reported previously: Laucht, Esser, & Schmidt, 1997; Laucht et al., 2000). Only firstborn children with singleton births and German-speaking parents were enrolled in the study. Assessments were conducted at the ages of 3 months and 2, 4.5, 8, 11, 15 and most recently at age 19 years. Of the initial sample, 18 participants (4.7%) were excluded because of severe handicaps (IQ or MQ < 70 or neurological disorder) and 37 (9.6%) were dropouts. The present investigation included 325 young adults (151 males, 174 females) who participated in the 19-year assessment and for whom CBCL data at age 8 or 11 and information about psychopathology were available. The study was approved by the ethics committee of the University of Heidelberg and written informed consent was obtained from all participants.

Assessments. At ages 8 and 11 parents completed the German version of the Child Behavior Checklist (CBCL/4–18; Achenbach, 1991). The CBCL presents descriptions of 118 problem behaviors which are likely to occur in children aged 4 to 18 years. Eight narrow-band syndrome scales can be calculated, indicating withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. Standard T-scores provide a guideline as to whether the child is scoring low or high on the syndrome scales relative to other children of the same age and gender. A T-score of 50 indicates average functioning and every 10 points represents one standard deviation. In the present study, the CBCL-DP was used as a linear scale: T-scores of the three subscales attention problems, aggressive behavior and anxious/depressed were summed to form the *CBCL dysregulation profile* (CBCL-DP) score and were averaged for the 8- and 11-year assessment. In 31 participants, CBCL information was available only once (missing CBCL: $n = 24$ at 8 years; $n = 7$ at 11 years).

The Mannheim Parent Interview (MEI; Esser, Blanz, Geisel, & Laucht, 1989) was conducted to obtain psychiatric diagnoses at age 8 years. The MEI is a highly structured interview adapted from Rutter's parent interviews (Cox & Rutter, 1985), which was modified to include all symptoms related to major DSM-IV diagnoses. The MEI has been shown to be a sensitive measure of child disturbance (Laucht et al., 1997; Laucht, Esser, & Schmidt, 2001). In addition, the Scales for Levels of Functioning (Marcus, Blanz, Esser, Niemeyer, & Schmidt, 1993) were used to evaluate global adaptation of the children to developmental demands irrespective of psychopathology. Based on expert ratings, these seven-step (1 = low; 7 = high) scales aim to measure functioning in family, performances, peer relationships, interests and autonomy.

Information about parental education and family income was obtained in a standardized parent interview conducted at the 8-year assessment. *Low parental education* was coded for parents without educational qualification or without skilled job training.

At age 19 years, the Structured Clinical Interview for DSM-IV (SCID-I; Wittchen, 1997) was administered to assess young adults' *psychiatric disorders* by trained psychologists who were blind for past CBCL profiles. Diagnoses refer to a time interval of the past 4 years prior to and including the current assessment. In addition, overall psychological functioning was evaluated on the Global Assessment of Functioning scale (GAF; Saß, Wittchen, & Zaudig, 2001). To assess *smoking status* and frequency, the young adults completed a smoking inventory which is part of the Substance Use Questionnaire designed by Müller and Abbet (1991) in collaboration with the World Health Organization. The degree of *nicotine dependence* was measured with the Fagerström Test for Nicotine Dependence (FTND; Heatherton Kozlowski, Frecker, & Fagerström, 1991). Young adults were also administered the Beck Depression Inventory (BDI; Hautzinger, Bailer, Worall, & Keller, 1994), measuring self-reported severity of depressive symptoms, and the Munich Events List (MEL; Maier-Diewald Wittchen, Hecht, & Werner-Eilert, 1983), which asks for the occurrence of stressful life events and chronic difficulties during the period of years until the last assessment. Both instruments include items assessing suicidal behavior. *Suicidal ideation* was coded if the participants agreed with the BDI statements 'I have thoughts of killing myself, but I would not carry them out,' 'I would like to kill myself,' or 'I would kill myself if I had the chance.' Within the MEL participants were asked directly if they had made a *suicide attempt*.

Data analysis

Correlation analysis was used to determine the associations of CBCL-DP with gender, family income, parental educational level, level of functioning and psychiatric diagnosis at age 8 years. Gender differences regarding psychiatric diagnosis, nicotine dependence, suicidal behavior and overall psychological functioning at age 19 years were tested with Chi square and Mann–Whitney U-tests. Logistic and linear regression models were performed to examine the association between CBCL-DP and psychiatric outcome in young adulthood. The level of significance adopted for all analyses was 5%. Parental education and family income and gender were introduced as covariates to estimate the effect of the CBCL-DP score independent of these potential confounders. To clarify whether the effect of CBCL-DP results from its association with a poorer level of functioning or with the persistence of psychiatric disorders at age 8 years, the models were additionally adjusted for these variables in a second step. Missing data of family income and suicidal ideation ($n = 2$ and $n = 1$ cases, respectively) were replaced by the group mean. In one case, information about parental education at age 8 years was not available and was therefore replaced by the information from the most recent assessment (age 4.5 years). To examine whether CBCL-DP scores would be particularly predictive of either the development of psychiatric comorbidity, in general, or the co-occurrence of specific disorders, all participants fulfilling the criteria of at least two Axis I disorders were grouped into those with a single and those with two or more comorbid disorders. In addition, two subgroups were formed indicating the co-occurrence of substance use disorders with mood or anxiety disorders and the comorbidity of cannabis and alcohol use disorders.[1]

[1] Prevalences were too low to analyze additional comorbid existing disorders.

Table 1 Descriptive sample characteristics as associated with CBCL-DP score

		r [1]	p
Gender (male), *N* (%)	151 (46.5)	.065	.242
Low parental education, *N* (%)	51 (15.7)	.109	.051
Per capita income (DM per month), *M* (*SD*)	1461.9 (806.8)	−.118	**.033**
Psychiatric disorder at 8 years, *N* (%)	84 (25.8)	.498	**<.001**
Level of functioning, *M* (*SD*)	18.6 (2.5)	−.413	**<.001**

[1]Point biserial and Pearson correlations, respectively.

Results

Sample characteristics

While gender was unrelated to CBCL-DP, significant correlations with family income, psychiatric diagnosis and the child's level of functioning and a trend toward association with parental education were observed (Table 1). Along with higher CBCL-DP values, the probability of any DSM-IV diagnosis at age 8 increased and the level of functioning decreased. In addition, families of offspring with high CBCL-DP values were characterized by lower income and a higher rate of low-educated parents.

In young adulthood, *N* = 75 (23.0%) of the overall sample met criteria for at least one DSM-IV disorder. Table 2 depicts the 4-year prevalences in detail, including the number of cases reporting suicide attempts or acute suicidal ideation and mean nicotine dependence and global functioning scores. Almost one-third of the sample reported daily smoking (*N* = 94) and *N* = 57 (17.5%) reported low to very strong nicotine dependence as indicated by the FTND scores (values between 3 and 10). Significant differences in gender distribution emerged in mood disorders, with higher rates of major depression in females than in males. There were no gender differences with regard to any other disorder, suicidal behavior, severity of nicotine dependence, and level of global functioning.

Table 2 Four-year prevalences of psychiatric disorders, global functioning and nicotine dependence in young adults by gender

	N (%)	Males *N* (%)	Females *N* (%)
Anxiety disorders	22 (6.8)	8 (5.3)	14 (8.0)
Mood disorders	24 (7.4)	3 (2.0)	21 (12.1)**
Suicidal ideation	36 (11.0)	14 (9.3)	22 (12.6)
Suicide attempt	14 (4.3)	4 (2.6)	10 (5.7)
Conduct disorder	9 (2.8)	7 (4.6)	2 (1.1)
ADHD	8 (2.5)	5 (3.3)	3 (1.7)
Alcohol abuse/ dependence	15 (4.6)	10 (6.6)	5 (2.9)
Cannabis abuse/ dependence	29 (8.9)	18 (11.9)	11 (6.3)
Somatoform disorders	5 (1.5)	0 (0)	5 (2.9)
Eating disorders	5 (1.5)	0 (0)	5 (2.9)
FTND scale: *M* (SD)	.9 (1.9)	1.1 (2.1)	.8 (1.7)
GAF scale: *M* (*SD*)	77.1 (11.2)	76.6 (11.2)	77.5 (11.3)

FTND = Fagerström Test for Nicotine Dependence, GAF = Global Assessment of Functioning.
**p < .001 Fisher exact test for gender differences.

As can be seen in Table 3, CBCL-DP scores between 8 and 11 years significantly predicted several of the psychiatric outcomes assessed at age 19 years, even after adjustment for parental education and family income. The higher their CBCL-DP score, the more increased was the risk for ADHD, mood and substance use disorders in young adults at age 19 years. Moreover, suicidal ideation, suicidal attempt, higher FTND scores and poorer overall functioning at age 19 were significantly more prevalent with increasing CBCL-DP scores. In contrast, there were no significant associations with anxiety disorders, conduct disorder, and eating or somatoform disorders at age 19 years.[2] None of the young adults was diagnosed with bipolar disorder. Furthermore, Table 4 shows that higher CBCL-DP scores were unrelated to young adults' comorbidity in general. Participants with any co-occurring disorder were not characterized by higher CBCL-DP scores compared to participants with one single psychiatric diagnosis. Likewise, the co-occurrence of substance use disorders with mood or anxiety disorders was not significantly predicted by the CBCL- DP score between age 8 and 11 years. In contrast, CBCL-DP scores were significantly higher in participants with comorbid cannabis and alcohol use disorders. Family income and low parental education during childhood were unrelated to the risk of psychiatric outcome or level of global functioning in young adulthood. Adjustment for psychiatric disorders that had already emerged at age 8 years resulted in weakening of the predictive value of the CBCL-DP score for young adults' ADHD diagnosis (p = .140) and mood disorders (p = .077) (Table 5). Likewise, after adjustment for the level of functioning as an indicator of impairment at age 8 years, the predictive value of the CBCL-DP score for young adults' ADHD diagnosis (p = .057) and mood disorders (p = .078) no longer reached statistical significance (see Supplementary Table s3).

Discussion

This longitudinal study found evidence that young adults with higher CBCL-DP scores in childhood are at increased risk for attention deficit/hyperactivity disorder (ADHD), mood and substance use disor-

[2] Please note that the study sample was enriched with children born at risk. To provide some evidence as to whether the results might be generalized to the general population, regression models were also adjusted for the number of psychosocial and biological risk factors. Considering these factors, the CBCL-DP score no longer significantly predicted young adults' depression and suicidal behavior, whereas the other results remained unchanged.

Table 3 Predicting young adults' diagnostic outcomes from CBCL-DP score, controlling for parental education and per capita income[1]

	CBCL-DP		Low parental education		Per capita income (DM per month/100)	
Outcome at age 19 years	*B (SE)*	*p*	*B (SE)*	*p*	*B (SE)*	*p*
Anxiety disorders	−.01 (.02)	.48	.22 (.60)	.72	−.01 (.03)	.99
Mood disorders	**.03 (.01)**	**<.01**	.38 (.57)	.51	.01 (.02)	.53
Conduct disorder	.01 (.02)	.45	−.01 (.87)	.99	−.08 (.07)	.28
ADHD	**.05 (.02)**	**<.01**	−.60 (1.15)	.60	.04 (.03)	.25
Alcohol abuse/dependence	**.05 (.01)**	**<.01**	−.47 (.83)	.57	.01 (.04)	.86
Cannabis abuse/dependence	**.03 (.01)**	**<.01**	.48 (.50)	.34	.01 (.03)	.85
Somatoform disorders[2]	−.02 (.04)	.15	.47 (n.a.)	1	.02 (.03)	.29
Eating disorders[2]	−.05 (.05)	.26	.28 (n.a.)	1	.01 (.04)	.70
Suicidal ideation	**.03 (.01)**	**<.01**	−.51 (.57)	.37	.01 (.02)	.56
Suicidal attempt	**.03 (.01)**	**.04**	.55 (.66)	.40	−.04 (.06)	.48
FTND score: *M (SD)*	**.02 (.01)**	**<.001**	.52 (.29)	**.07**	−.02 (.01)	.18
GAF scale: *M (SD)*	**−.26 (.04)**	**<.001**	−2.91 (1.62)	**.07**	.09 (.07)	.24

FTND = Fagerström Test for Nicotine Dependence, GAF = Global Assessment of Functioning.
[1]Values adjusted for gender.
[2]Median unbiased estimates from exact logistic regression.

Table 4 Predicting young adults' comorbidity from CBCL-DP score, controlling for parental education and per capita income.[1, 2]

	CBCL-DP		Low parental education		Per capita income (DM per month/100)	
Comorbidity of	*B (SE)*	*p*	*B (SE)*	*p*	*B (SE)*	*p*
Any psychiatric disorder	−.02 (.01)	.146	−.02 (.66)	.98	−.00 (.04)	.96
Substance use disorders with anxiety or mood disorder	−.01 (.02)	.99	1.36 (.83)	.10	−.04 (.08)	.59
Cannabis and alcohol use disorders	**.04 (.02)**	**<.05**	−1.02 (1.05)	.33	−.07 (.07)	.27

[1]Sample includes $N = 75$ participants meeting the criteria for at least one DSM IV disorder in young adulthood.
[2]Values adjusted for gender.

Table 5 Predicting young adults' diagnostic outcomes from CBCL-DP score, controlling for psychiatric disorder at age 8[1, 2]

	CBCL-DP		Previous psychiatric disorder	
Outcome at age 19 years	*B (SE)*	*p*	*B (SE)*	*p*
Anxiety disorders	−.02 (.02)	.37	−.36 (.58)	.53
Mood disorders	.02 (.01)	.08	.56 (.55)	.31
Conduct disorder	.02 (.02)	.41	−.29 (.87)	.74
ADHD	.03 (.02)	.15	**2.72 (1.21)**	**.03**
Alcohol abuse/dependence	**.04 (.02)**	**<.01**	.25 (.70)	.72
Cannabis abuse/dependence	**.04 (.01)**	**<.01**	−.64 (.53)	.23
Somatoform disorders	−.07 (.05)	.15	2.03 (1.12)	.21
Eating disorders	−.05 (.05)	.30	.10 (1.13)	.99
Suicidal ideation	**.03 (.01)**	**.03**	.01 (.47)	.98
Suicidal attempt	**.04 (.02)**	**.01**	−1.36 (.83)	.10
FTND score: *M (SD)*	**.02 (.01)**	**<.01**	−.07 (.27)	.80
GAF scale: *M (SD)*	**−.17 (.04)**	**<.001**	**−6.48 (1.49)**	**<.001**

[1]All models are adjusted for parental education and per capita income.
[2]Values adjusted for gender.

ders, suicidality, and poorer overall functioning. The higher their CBCL-DP score, the more increased was the risk at age 19 years. Our findings suggest that in many cases, impairing psychopathology similar to what was expressing itself in the childhood behavioral phenotype is a likely outcome in young adulthood. However, the CBCL-DP did not predict mood disorders and ADHD if these disorders at baseline are controlled for. The same applies to impairment at baseline, suggesting that CBCL-DP may function, at least in part, as a marker of severity. Still, severe dysregulation remained predictive of suicidality, substance use and impairment even when baseline symptoms were controlled. Of note, the CBCL-DP did not predict bipolar disorder.

Childhood dysregulation may, however, take different developmental trajectories and, therefore, the behavioral phenotype captured by the CBCL-DP is not simply an early manifestation of a single disease process. In cross-sectional studies severe dysregulation and related phenotypes in childhood are associated with comorbidity between internalizing and externalizing disorders (e.g., Stringaris & Goodman, 2009). Longitudinally, childhood dysregulation was a precursor neither of a specific pattern of comorbidity nor of comorbidity in general: it did not predict the joint occurrence of disorders, but showed an independent association with various 'pure' disorders. Thus, the developmental course of dysregulation may not be an example of heterotypic continuity (Angold et al., 1999). Rather, severe

dysregulation seems to represent an early risk marker of a persisting deficit of self-regulation of affect and behavior underlying different psychiatric disorders.

Severe dysregulation was associated with low family income, psychiatric diagnoses and a low level of functioning cross-sectionally. While there is mounting evidence that severe dysregulation is related to impairment and severe psychopathology, concurrently and across time, investigators seldom have examined whether different aspects of dysregulation relate in the same manner. Data from latent class analysis (Althoff, Rettew, Faraone, Boomsma, & Hudziak, 2006) and behavior genetics studies (Boomsma et al., 2006; Hudziak, Althoff, Derks, Faraone, & Boomsma, 2005) have shown that the CBCL-DP is distinct from each of its components (i.e., attention problems, anxious/depression, and aggression) either alone or in tandem. Future studies need to test whether different patterns of variation within the components of the CBCL-DP account for the different developmental trajectories (Lahey et al., 2008).

Likewise, it is possible that individual differences in dysregulation and young adult psychopathology are caused by some other factor(s) and that dysregulation does not have direct causal effects on later psychopathology. Future investigations will, therefore, need to lay particular emphasis on mediating and moderating influences of particular symptoms underlying dysregulation such as persistent irritability, emotional overreactivity, or lack of effortful control (Rothbart & Bates, 2006).

With regard to biological markers of the CBCL-DP, previous research has provided useful initial hints that alterations in the serotonin system may be relevant in some CBCL-DP children (Zepf et al., 2008); others have reported evidence for the importance of both genetic and shared environmental factors (Hudziak et al., 2005). Psychosocial mediating mechanisms seem likely to be involved in transitions from severe dysregulation to different forms of psychopathology. Children with dysregulation may behave in ways that predispose to life situations that provide risks for other disorders (Lahey et al., 2008).

The observed lack of comorbidity at follow-up may, on the other hand, be a methodological artifact. Dysregulation may not have emerged as a risk factor for later comorbidity due to the measures applied: while the baseline assessment used a dimensional characterization (i.e., the CBCL-DP), the outcome in young adulthood was primarily categorical (DSM-IV diagnoses). Since it has been shown that DSM categories inadequately capture the range and severity of some forms of adolescent psychopathology (Hudziak, Achenbach, Althoff, & Pine, 2007), our approach may have missed subclinical comorbid cases and thus underestimated the true extent of comorbidity. In line with the proposed DSM-V, future longitudinal studies may benefit from considering dimensional outcome characterizations (Ayer et al., 2009).

Our findings are in line with previous findings from temperament and personality psychology suggesting that severe dysregulation in childhood can set the stage for later severe psychiatric illness (Buss & Plomin, 1984; Caspi, 2000; Rothbart & Bates, 2006). In a short-term longitudinal study in a clinical sample, the CBCL-DP during middle childhood predicted considerable psychosocial impairment at late adolescent follow-up (Hazell, Carr, Lewin, & Sly, 2003). Moreover, the results of our study show striking similarities with the two previous studies on the long-term outcome of CBCL-DP (Meyer et al., 2009; Biederman et al., 2009), in that all three studies observed heightened rates of psychiatric disorders, an increased risk for suicidality, and marked psychosocial impairment at young-adult follow-up. Higher rates of depression were observed correspondingly in the Biederman cohort and our sample. Meyer et al. (2009), in their sample at risk for mood disorders, also reported high rates of depression but the risk in the CBCL-DP group was not elevated significantly due to the high rates in offspring without the CBCL-DP. For the same reason, the high rates of substance use disorders in both US studies did not reach statistical significance. As Meyer et al. (2009) noted, this is different from concluding that those conditions do not represent a frequent hazard in the two samples.

Various studies have examined behavioral phenotypes, such as emotional or mood lability and affective instability, that are closely linked to the concept of severe dysregulation. In a recent cross-sectional community study, mood lability has been shown to be a shared risk factor for both internalizing and externalizing disorders (Stringaris & Goodman, 2009). Within the longitudinal design of the Dunedin study, Caspi (2000) examined the influence of early-appearing temperamental differences for life-course development. Young children who were impulsive, restless, negativistic, distractible, and labile in their emotional responses ('uncontrolled temperament') were more likely to be diagnosed with alcohol dependence and suicidality and were characterized by high levels of impulsivity in young adulthood. Longitudinal data from the Great Smoky Mountains Study (Brotman et al., 2006) suggest that children who meet criteria for severe mood dysregulation (SMD), characterized by chronic, non-episodic irritability and hyperarousal, are significantly more likely to be diagnosed with a depressive disorder in young adulthood. This finding is consistent with other literature showing associations between chronic irritability in youth and depression in early adulthood (Burke, Loeber, Lahey, & Rathouz, 2005; Stringaris, Cohen, Pine, & Leibenluft, 2009).

The common appearance and clinical importance of severe dysregulation, however, coexist with vari-

ous concerns. The almost interchangeable use of terms such as mood lability, emotional impulsiveness, SMD, and severe dysregulation in parts of the current literature may impede a critical analysis regarding their viability as scientific constructs (Cole, Martin, & Dennis, 2004). It remains to be clarified whether the suggested introduction of a new diagnostic category for temper dysregulation disorder with dysphoria into the Mood Disorders Section of DSM-V fosters a more careful conceptualization and rigorous measurement of these complex constructs (Althoff, 2010).

One issue that has received considerable attention in the child psychiatry literature is whether severe dysregulation should be considered a developmental presentation of bipolar disorder (BD; Holtmann et al., 2010b). While the CBCL-DP is commonly seen in children with BD (Biederman et al., 1995), the specificity of the association with mania has come into question (Diler et al., 2009; Holtmann, Bölte, Goth, & Poustka, 2008; Volk & Todd, 2007). Neither youth with SMD nor those with related phenotypes seem to be at risk for developing episodic BD (Brotman et al., 2006; Leibenluft et al., 2006; Stringaris et al., 2009, 2010). Likewise, in our cohort the CBCL-DP was not associated with BD at follow-up. In contrast, both longitudinal US studies showed a transition of CBCL-DP to BD in young adulthood in about every third subject. However, the different outcomes may in part be attributed to sampling differences. The cohort in the study provided by Biederman et al. (2009) consisted of referred ADHD youth and may not generalize to the context outside of ADHD. In addition, 11% of their CBCL-DP positive group already exhibited 'subthreshold BD' at baseline. Meyer et al. (2009) studied a sample at high risk for mood disorders, and it was not until the young-adult follow-up (at a mean age of 21.7 years) that the CBCL phenotype was found to predict BD. Our sample was examined at age 19. We cannot rule out the possibility that, despite the absence of current BD in our sample, a higher CBCL-DP score may be indicative of a future risk of BD. BD most often begins with depressive episodes (Duffy, Alda, Hajek, Sherry, & Grof, 2010), and at least 10% of adolescent patients with initial unipolar depression develop (hypo)mania during the next decade of their life (Beesdo et al., 2009). It is possible that some former CBCL-DP children with a current depressive disorder are actually experiencing the onset of BD in the form of a depressive episode and that these young adults ultimately will develop manic episodes later in life.

Several limitations should be considered when interpreting the findings of the study. First, since our study sample was enriched with children born at risk, it is possible that the CBCL-DP children identified in this study might differ from those seen in both general population and clinical settings. To provide some evidence as to whether the results might be generalized to the general population, regression models were also adjusted for the number of psychosocial and biological risk factors. Considering these factors, the CBCL-DP score no longer significantly predicted young adults' depression and suicidal behavior, whereas the other results remained unchanged. Second, the absolute numbers of psychiatric disorders at follow-up were low, limiting conclusions for associations with individual disorders. Third, all three available long-term studies on CBCL-DP used high-risk or clinical samples. Therefore, there is need for studies in general populations.

The main strengths of this study are the longitudinal prospective design, the low attrition rate, and the use of a widely used, standardized parental questionnaire with excellent psychometric properties at baseline and the use of a structured clinical interview and other established measures at follow-up.

Clinical implications

If replicated in population-based studies, our findings may have important clinical implications. If a child psychiatrist is evaluating a youngster with a mixed phenotype of coexisting attention and behavior problems and anxious-depressed symptoms, it should be noted that these childhood problems may predict serious psychopathology in young adulthood, although it is impossible to predict the precise nature of the later disorders. Screening and finding at-risk children and developing effective intervention strategies to change their often deteriorating development are important challenges for child mental health efforts. Until now, no treatment trials have been published for children with severe dysregulation as captured by the CBCL-DP. Clinicians and researchers should refrain from using the CBCL-DP as a measure of BD. Our findings add to considerations to use dimensional measures to assess developmental psychopathology, and therefore may have important implications for refinements of future child psychiatric classification and DSM-V or ICD-11.

In conclusion, youth with CBCL-DP in childhood are more likely than comparison subjects to meet criteria for substance use, and suicidal ideation and suicide attempts in young adulthood. In addition, they show a marked impairment of overall functioning, suggesting that severe dysregulation might be an early developmental risk factor of severe psychopathology.

Supplementary Material

The following supplementary material is available for this article:

Sampling procedure (Word document)

This material is available as part of the online article from:

http://www.blackwell-synergy.com/doi/abs/10.1111/j.1469-7610.2010.01458.x

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Key points

- Severe affective and behavioral dysregulation as captured by the Child Behavior Checklist-Dysregulation Profile affects 1–2% of youth in epidemiological samples, 6–7% in child psychiatric clinical samples and 13–20% of children with attention-deficit/hyperactivity disorder.
- Youth with behavioral and affective dysregulation in childhood are at increased risk for substance use, suicidal ideation and suicide attempts, and impairment in young adulthood.
- Different developmental trajectories suggest that the CBCL-DP is not simply an early manifestation of a single disease process but rather a developmental risk marker of a persisting deficit of self-regulation of affect and behavior.

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