Dysregulation profile within categorical disorders - comparison between clinical groups

TITLE

Dysregulation profile (DP) as a transdiagnostic psychopathological factor in clinically referred children – comparisons between disorders and latent structure

AUTHOR NAMES AND AFFILIATIONS

Biyao Wang[1,2*], Andreas Becker[1*], Christina Kaelble[1], Aribert Rothenberger[1], Henrik Uebel-von Sandersleben[1]

[*]joint first authors

[1]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center of Goettingen, Goettingen, Germany

[2]Department of Clinical, Educational and Health Psychology, University College London, London, UK

CORRESPONDING AUTHOR

Biyao Wang

Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center Goettingen

von-Siebold-Str. 5, 37075 Goettingen, Germany

Biyao.Wang@med.uni-goettingen.de

Dysregulation profile within categorical disorders - comparison between clinical groups

ABSTRACT

Background: Dysregulation Profile (DP) describes the psychopathological construct of concurrent impairments in the ability to regulate emotion, behaviour, and cognition measured by the Child Behaviour Checklist (CBCL). Such transdiagnostic dimensions of psychopathology play an important role in addition to core symptoms of psychiatric diagnosis in clinical practice. Evaluation of DP in children with different mental disorders may improve our understanding and treatment of both contents.

Methods: 911 clinically referred children between 6 and 18 years were investigated. The sample consisted of five 'pure' disorders groups, i.e., tic disorder (TIC), anxiety disorder, obsessive compulsive disorder, depression, Attention Deficit Hyperactivity Disorder (ADHD), and two comorbid disorder group, i.e., ADHD + TIC and ADHD + oppositional defiant disorder (ODD). DP level and latent structure were compared across groups.

Results: The rate of severe/abnormal dysregulation rates varied from 15 % to 44 % when the 210 cut-off was used, and 5 % to 18 % when stringent cut-off was used (i.e. ->70 on all DP-subscales). The most affected population were children with comorbid ADHD with ODD/TIC, while least were those with TIC only. Five different latent phenotypes of DP were found.

Conclusion: DP above clinical cut-off level widely exists in clinically referred children in parallel to core symptoms of their diagnosis, especially among children with comorbidities. During clinical assessment it would be worth to clarify the role of DP-related problems within the general psychosocial impairment of the patient to improve a personalized approach.

Key words: Dysregulation profile; transdiagnostic factor; children; Child Behaviour Checklist; latent class analysis

Dysregulation profile within categorical disorders - comparison between clinical groups

Transdiagnostic dimensions of psychopathologies, such as sleep problems, play an important role in clinical practice in addition to core psychiatric disorders, such as Attention Deficit Hyperactivity Disorder (ADHD). The concurrent impairments in the ability to regulate emotion (anxiety, depression), behaviour (aggression), and cognition (attention problems), is an emerging phenotype of such transdiagnostic dimensions of psychopathologies. This phenotype of broad-based, generalized emotional and behavioural dysregulation is referred as the Dysregulation Profile (DP, R. R. Althoff, Rettew, Ayer, & Hudziak, 2010; Ayer et al., 2009). Rooting from the controversies with pediatric/juvenile bipolar disorder (Faraone, Althoff, Hudziak, Monuteaux, & Biederman, 2005; M Holtmann, Goth, Wöckel, Poustka, & Bölte, 2008), DP was firstly (and universally) measured by elevated scores on three syndrome scales of the Child Behaviour Checklist: Anxious/Depressed (AD), Aggressive Behaviour (AGG), and Attention Problems (AP), and therefore sometimes referred as the AAA scale. While drawing increasing interest in research and clinical practice, dysregulation-related impairments have been added to the most recent versions of classification of mental disorders. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) included Disruptive Mood Dysregulation Disorder (F34.8) under the depressive disorders section to characterize children with severe irritability and anger (American Psychiatric Association, 2013). The 11th Revision of International Classification of Diseases (ICD-11) included oppositional defiant disorder with chronic irritability-anger (6C90.0) under disruptive behavior or dissocial disorders as a form of Oppositional Defiant Disorder (ODD) characterized by prevailing, persistent angry or irritable mood (World Health Organization, 2018). The variability of classifications including deficiency of self-regulation reflects its multi-faceted nature and comorbid existence.

The clinical meaning of DP is still debated, yet studies have shown that the manifestation of this multi-dimensional psychopathology is best conceptualized as a broad, overarching dysregulation syndrome, which exists over and above anxiety/depression, aggression, and inattention as specific problems (Deutz, Geeraerts, van Baar, Deković, & Prinzie, 2016; Geeraerts et al., 2015). Moreover, evidence from twin studies showed that the DP is highly heritable (R. R. Althoff, Rettew, Faraone, Boomsma, & Hudziak, 2006; Hudziak,

Althoff, Derks, Faraone, & Boomsma, 2005) and stable throughout childhood and adolescence probably due to genetic factors (Biederman et al., 2009; Boomsma et al., 2006; Nobile et al., 2016), and suggested that the influence of DP may persist into adulthood or even throughout the lifespan. It has consistently been shown to be associated with considerable psychosocial impairments and adverse outcomes such as suicidality and substance use (Robert R Althoff, Verhulst, Rettew, Hudziak, & van der Ende, 2010; Ayer et al., 2009; De Caluwé, Decuyper, & De Clercq, 2013; M. Holtmann et al., 2011) and to be an indicator of disordered self-regulation and impaired functioning (Bellani, Negri, & Brambilla, 2012; Jucksch, Salbach-Andrae, Lenz, Goth, Dopfner, et al., 2011). Severe dysregulation occurs in about 1-5% of children and adolescents in epidemiological samples (Robert R Althoff et al., 2010; Martin Holtmann et al., 2007; Hudziak et al., 2005; Volk & Todd, 2007). The rates reported from clinic-referred samples are higher with large discrepancy due to different settings or criteria considered, such as inpatient/outpatient status, gender ratio, age range, type of existing psychiatric disorders, cut-off score used or latent grouping method applied. For example, using the criteria based on a sum of T-scores, deficient emotional self-regulation (DESR) as an aggregate cut-off score of >180 but <210 (elevation of 1 Standard Deviation) on the AAA scales of the CBCL and Severe Dysregulation as an aggregate cut-off score of ⩾210 (elevation of 2 Standard Deviations or more). Biederman and colleagues examined 197 children with ADHD aged 6-18 years, and found 36% of them had a positive DESR and 19% had a positive Severe Dysregulation (Biederman, Petty, et al., 2012). Masi and colleagues found in a sample of 108 clinic-referred children with disruptive behaviour aged 9 to 15 years (16.7% girls), among whom 52.7% met the criteria for DESR and 38.79 % met the criteria for Severe Dysregulation (Masi, Muratori, Manfredi, Pisano, & Milone, 2015). In a sample of 348 children aged 6-12 years who were clinic-referred for assessment and treatment because of disruptive behaviour, Aitken and colleagues found about half of them (46.8%) met the criteria for Severe Dysregulation (Aitken, Battaglia, Marino, Mahendran, & Andrade, 2019). If they also applied a more stringent criteria of T-scores ⩾ 70 on all AAA scales, a lower rate of 15.2% was found. Using the same stringent criteria, Holtmann reported in a clinical sample of 939 children and adolescents (83.1% outpatients, 32.7% girls, 4-18 years old), that 6.6% met the criteria of this phenotype (M Holtmann et al., 2008), while Jucksch examined 9024 children and

adolescent aged 4 to 18 years old (35.7% girls) and found the rate of DP was 4.1% (3.5% of outpatients, 5.8% of inpatients) (Jucksch, Salbach-Andrae, Lenz, Goth, Döpfner, et al., 2011). Although DP was more frequently found/examined in children with externalizing disorders, such as ADHD and ODD, previous studies also found comorbidities of DP and internalizing disorders, such as anxiety disorders (R. R. Althoff, 2010; Biederman et al., 1995; Faraone et al., 2005; M Holtmann et al., 2008). Moreover, symptoms of DP overlapped and confounded with many more psychiatric disorders, with deficient self-regulation of different kinds being the most impairing component, such as deficiency of regulating behaviours in tic disorder and obsessive-compulsive disorder, deficiency of regulating emotions in anxiety disorder and depression, deficiency of regulating cognition in ADHD. The presence of comorbid DP will not only increase the impairments in patients and burdens of their families, but also will interfere with the effectiveness of treatment. Hence, evaluation of DP with different psychiatric disorders has great practical relevance, which may improve our understanding and estimation of this transdiagnostic dimension of psychopathologies in clinical setting, and thus provide better insight to personalized therapeutic approaches of patients' problems.

In the present study, we aimed to evaluate the presence of DP in a sample of clinically referred children who were diagnosed with different psychiatric disorders according to ICD-10 (WHO 1992). To our knowledge, very few studies have examined DP in a wide range of common clearly separated clinical groups and compared the rate of DP among them (Jucksch, Salbach-Andrae, Lenz, Goth, Dopfner, et al., 2011; Masi, Pisano, Milone, & Muratori, 2015). Also, in contrast to earlier studies, we selected "pure" disorders to avoid psychopathological confounders and controlled for the latter in two practically relevant cases of clearly defined comorbidity. Moreover, we measured DP with the AAA scale from the psychopathological screener CBCL by applying multiple relevant clinical cut-offs. We aim to characterize and compare children with different psychopathological complains to find out the more/less affected clinical groups. Also, the latent structure of DP was further investigated with latent class analysis, aiming to find latent phenotypes of DP and thus shed light on DP heterogeneity, which could assist our understanding of the co-occurrence of DP and core symptoms of a categorical disorder with respect to psychosocial impairment and personalized

Dysregulation profile within categorical disorders - comparison between clinical groups

treatment approaches.

MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURES

Participants were selected via a chart review; included were 911 children and adolescents (27.1% girls) between 6 and 18 years (mean age = 10.8, SD = 3.02 years). They were consecutive referrals (68.7% outpatients and 31.3% inpatients) assessed, diagnosed and treated between 2005 and 2015 in the Clinic for Child and Adolescent Psychiatry and Psychotherapy at the University Medical Center of Goettingen, Germany. A set of psychometrically valid questionnaires was sent by mail to the parents and patients about four weeks before their first appointment in the clinic. Parents filled in these psychopathological screenings at home, including the CBCL. Clinical assessment was performed with a two-step procedure. First, each patient firstly met a physician or psychologist advanced in training for child and adolescent psychiatry/psychotherapy for a clinical interview. Afterwards a preliminary diagnosis was given. In a second step, two senior, board certified specialists of the clinic (senior physician and senior psychologist) carried out a best-estimate case conference on the basis of the investigator reports and available documents/questionnaires and together determined the patient's formal diagnoses according to ICD-10 version 1993 (World Health Organization, 1993)**.** This study included patients who received formal diagnoses of the following types of common child psychiatric disorders:

(1) Tic disorders (TIC)

F95.0 Transient tic disorder

F95.1 Chronic motor or vocal tic disorder

F95.2 Combined motor and vocal tic disorder [de la Tourette's syndrome]

(2) Anxiety disorders:

Dysregulation profile within categorical disorders - comparison between clinical groups

F40.1 Social phobias

F40.2 Specific (isolated) phobias

F93.0 Separation anxiety disorder of childhood

F93.1 Phobic anxiety disorder of childhood

F93.2 Social anxiety disorder of childhood

F93.8 Other childhood emotional disorders

(3) Obsessive-compulsive disorder (OCD)

F42.0 Predominantly obsessional thoughts or ruminations

F42.1 Predominantly compulsive acts [obsessional rituals]

F42.2 Mixed obsessional thoughts and acts

(4) Depression

F34.1 Dysthymia [persistent depressive disorder]

(5) ADHD

F90.0 Disturbance of activity and attention [hyperkinetic disorder]

(6) Comorbid ADHD and TIC

Both criteria for hyperkinetic disorder (F90) and tic disorders (F95) were met

(7) Comorbid ADHD and ODD

F90.1 Hyperkinetic conduct disorder, both the general criteria for hyperkinetic disorder (F90) and conduct disorder (F91) were met

Based on the diagnoses they received, five groups of children received only one main/axis I diagnosis (i. e. no comorbidity) and were classified as 'pure' clinical disorders, i.e., TIC (n = 281), anxiety disorder (n = 137), OCD (n = 98), depression (n = 22), ADHD (n = 129). Two groups of children were diagnosed with two/comorbid disorders, i.e., comorbid ADHD and TIC (n = 52) and comorbid ADHD and ODD (n = 48). In addition, another group of children diagnosed with learning disorder (F81.0 specific reading disorder) but without psychiatric disorder was considered as clinical control (n = 144, 27.8% girls, mean age = 10.4, SD =

2.40 years). These procedures were approved by the local ethics committee (Ethics Commission of the University Medical Center of Goettingen) and written informed consent was given by all participants.

PSYCHOPATHOLOGICAL MEASURES

Dysregulation Profile measured by the Child Behaviour Checklist (CBCL-DP)

Child Behaviour Checklist (CBCL) is a standardized parent questionnaire of problem behaviour for children and adolescents (Achenbach, 1991). Child Behaviour Checklist Dysregulation Profile (CBCL-DP) was calculated from three CBCL subscales, namely Anxious/Depressed, Attention Problems and Aggressive Behaviour. Responses were rated on a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). Raw scores were converted to gender and age standard T-scores (M = 50 and SD = 10). Sum T-score of these three subscales was used to represent the children's and adolescents' levels of deficiency in self-regulation (range 150-300), with higher scores indicating higher levels of dysregulation. Severe Dysregulation was defined as positive by a score of $\geq$ 210 on the sum T-scores of Anxious/Depressed, Attention Problems and Aggressive Behaviour, deficient emotional self-regulation (DESR) was defined with a value between 180 and 209 (Biederman et al., 2009; Biederman, Spencer, et al., 2012; Faraone et al., 2005). The stringent criteria of DP was T-scores $\geqslant$ 70 on all Anxious/Depressed, Attention Problems and Aggressive Behaviour subscales.

STATISTICAL ANALYSES

Children's CBCL-DP sum T-score as well as Anxious/Depressed, Attention Problems and Aggressive Behaviour subscales T-scores were calculated and presented in a descriptive manner (i.e. means and standard deviations) according to the clinical groups they belong. Subsequently, pairwise comparisons between different clinical groups were made by means of analysis of variance (ANOVA) with following post-hoc tests to show the direction of differences. Then the number and rate of children classified as having clinically relevant level of CBCL-DP were presented descriptively according to their clinical groups and

using multiple cut-offs. The distribution of an abnormal dysregulation profile with clinical groups was examined with chi-squared tests.

Latent class analysis was additionally conducted to explore the potential heterogeneity in DP and psychopathologies. Latent class analysis is a useful tool for identifying a set of unobserved underlying subgroups (i.e., latent classes) of individuals based on their patterns of responses on variables (Lanza & Rhoades, 2013). The objective is to categorize people into classes using the observed items and identify items that best distinguish between classes (Nylund, Asparouhov, & Muthén, 2007). A series of solution with from one to six latent classes will be modelled and compared. Several criteria **were** taken into account to find the model which fit best to data.

Latent class analysis was performed using Mplus version 7.3. Other analyses were carried out using SPSS version 23. Missing data on the outcome variables were handled through full information maximum likelihood (FIML) estimation in Mplus as a standard procedure under the assumption of missing at random (Muthén & Muthén, 1998-2015).

RESULTS

DESCRIPTIVE STATISTICS

Average score CBCL-DP was 188.65 out of the total T-score of 300 (Table 1). From a descriptive manner, children depression and comorbid ADHD with TIC/ODD reported the highest levels of CBCL-DP. Lowest level of dysregulation appears in children with TIC, but the mean score was still far from the ones in the clinical control group. Children diagnosed as depression had the highest score on Anxious/Depressed, children diagnosed as comorbid ADHD and TIC had the highest score on Attention Problems, while children with comorbid ADHD and ODD had the highest score on Aggressive Behaviour. Children with TIC still had the lowest level of dysregulation on all three domains.

Dysregulation profile within categorical disorders - comparison between clinical groups

ABNORMAL RATE

The prevalence of severely dysregulated children and adolescents widely varied across groups and the criteria applied (Table 2). Approximately one-fifth of children were defined as having Severe Dysregulation, the rates nearly double in children defined as DESR. Using the stringent criteria of elevated scores on all Anxious/Depressed, Attention Problems and Aggressive Behaviour subscales, the rates dramatically dropped. Children with TIC had the lowest rates of abnormal DP, both defined with Severe Dysregulation and Stringent DP. Highest rate of Severe Dysregulation was found in children with comorbid ADHD and ODD, while the highest rate of Stringent DP was found in children with depression. When DESR status was considered in addition to Severe Dysregulation, more than half of children with any psychiatric disorder fall into these criteria, with 80% or more children in Depression and two comorbid group (ADHD with ODD/TIC). Chi-squared tests of independence were calculated comparing the frequency of having abnormal DP in different clinical groups. Results suggested that being defined as Severe Dysregulation ($\chi^2(7) = 62.185$, $p < 0.001$), Severe Dysregulation or DESR ($\chi^2(7) = 92.856$, $p < 0.001$) and Stringent DP ($\chi^2(7) = 26.180$, $p < 0.001$) were all significant different according to the psychiatric disorder children had. These interactions remained significant even when the clinical control group was removed (for Severe Dysregulation $\chi^2(6) = 25.921$, $p < 0.001$; for Severe Dysregulation or DESR $\chi^2(6) = 40.559$, $p < 0.001$; for Stringent DP $\chi^2(6) = 12.767$, $p = 0.047$).

LATENT STRUCTURE

Considering the inconsistency in mean scores and abnormal rates (partly mismatch in the ranking of different clinical groups), potential heterogeneity of DP was explored with latent class analysis (Table 3). Model with five latent classes was the best solution for DP on CBCL-subscale level (Figure 1). About half of children and adolescents were labelled as *Neglectable dysregulation* with mean CBCL-DP score of 168.01 and had mild affect and attention problem. About one-fifth of children and adolescents were labelled as *Moderate general dysregulation* with mean CBCL-DP score of 193.51 who had deficient level of affect,

attention, and behaviour difficulties. A small group of children and adolescents was labelled as*, Severe dysregulation with low aggressivity* with mean CBCL-DP score of 200.65 and considerate level of affect and attention problem but low level of aggressivity. Another one-fifth of children and adolescents were labelled as *Severe general dysregulation* with mean CBCL-DP score of 214.34 and concurrent high level of affect, attention, and behaviour difficulties. The smallest group was consisted of a twentieth of children and adolescents who were labelled as *Severe dysregulation with high aggressivity* with mean CBCL-DP score of 233.50, they had high level of affect and attention problems, and extremely severe aggressivity. Distribution of children and adolescents assigned to their most likely latent class based on the model were presented with their clinical groups (Figure 2). Abnormality of CBCL-DP status and the relationship with latent class of DP were presented in Table 4, with panel A showing abnormality of CBCL-DP by latent class and panel B showing latent class by abnormality of CBCL-DP. None of children classified as latent class *Neglectable dysregulation* fell into the criteria of Severe Dysregulation or Stringent DP, and none of children defined as Severe Dysregulation or Stringent DP were classified as latent class *Neglectable dysregulation.* Almost all of children classified as dysregulated by latent class analysis fell into the criteria of Severe Dysregulation or DESR (86.64% for *Moderate general dysregulation* class, 100% for *Severe dysregulation with low aggressivity* class, *Severe general dysregulation* and *Severe dysregulation with high aggressivity* class) with most children in *Moderate general dysregulation* class (76.04%) were defined as DESR. All children defined as Stringent DP fell into the *Severe general dysregulation* class or *Severe dysregulation with high aggressivity* class.

DISCUSSION

It was found that the DP seems to be a common transdiagnostic psychopathological factor in clinical practice with varying severity levels and abnormal rates even between children with different non-comorbid (“pure”) psychiatric diagnoses. The lowest average level of DP appeared in children with TIC. Such findings

are unlikely to be attributed to the inclusion of transient tic disorder (F95.0), which is considered less severe than chronic tic disorder (F95.1) or Tourette's syndrome (F95.2), since patients with transient tics only accounted for a very small proportion of the TIC group (n = 22, i.e. 7.8%). The highest average level of DP appeared in children with comorbid ADHD and ODD, but still fell into the borderline range of deficient emotional self-regulation (DESR) (Biederman, Spencer, et al., 2012; Faraone et al., 2005). As expected, children with different psychiatric disorders showed an elevated level of dysregulation in the very DP-sub-domain which corresponds to their core symptoms. For instance, children diagnosed with depression had the highest score on Anxious/Depressed, children with comorbid ADHD and TIC had the highest score on Attention Problems, while children with comorbid ADHD and ODD had the highest score on Aggressive Behaviour. The ranking of average DP severity in different clinical groups roughly corresponded with their abnormal rates (i. e. groups with higher CBCL-DP scores more or less resulted in higher abnormal rates). The rate of Severe Dysregulation (CBCL-DP ≥ 210) in the non-psychiatric clinical controls was within the rates of 1-5 % in epidemiological samples (Robert R Althoff et al., 2010; Hudziak et al., 2005), while the rate in any psychiatric groups was far beyond this range. Considering DESR (CBCL-DP above 180 but equal/below 210) as a borderline category, the rates were even more striking for but highly consistent with those reported in previous studies (Biederman, Petty, et al., 2012; Masi, Muratori, et al., 2015). Although the proportion only seemed to be less worrying when the most stringent criteria was used (Stringent DP, ≥ 70 on all Anxious/Depressed, Attention Problems and Aggressive Behaviour subscales of CBCL-DP), a finding echoing previous evidence (Aitken et al., 2019; M Holtmann et al., 2008; Jucksch, Salbach-Andrae, Lenz, Goth, Döpfner, et al., 2011), it suggested that a considerable number of children had considerable levels of dysregulation. Such deficit of self-regulation was multifaceted, with symptoms in all emotional, attentional and behavioural domains, and beyond their core diagnoses, remained largely overlooked, and barely treated. The comorbid groups of ADHD+ODD and ADHD+TIC were more strongly affected by DP. This vulnerability was featured with ADHD plus another disorder, which not only echoes with previous findings of the high risk of dysregulation in ADHD population (Copeland, Angold, Costello, & Egger, 2013; Mayes et al., 2015; Shaw, Stringaris, Nigg, & Leibenluft, 2014; van Stralen, 2016), but also addressed the

additional/interactive risk of both psychopathologies. To be noted, the comorbid group of ADHD+TIC did not have an intermediate effect of 'pure' group of ADHD and 'pure' group of TIC, but showed an accumulative effect, which corresponds to the additive model of the factors ADHD and TIC (Roessner, Becker, Banaschewski, & Rothenberger, 2007) and supports the notion that, when TIC is added to ADHD, it does not change much to the disturbances of ADHD (Rothenberger & Roessner, 2013).

Surprisingly, children with similar level of average DP scores had a wide range of abnormal rates, suggesting hidden heterogeneity in the population and therefore was further investigated by latent class analysis. Five different latent phenotypes (DP-subgroup-profiles) could clearly be differentiated by scores of Anxious/Depressed, Attention Problems and Aggressive Behaviour which corresponded with emotion, cognition and behaviour sub-domains of DP. Those children classified in the four clearly dysregulated latent classes (*Moderate general dysregulation, Severe general dysregulation, Severe dysregulation with low aggressivity, Severe dysregulation with high aggressivity*) had clearly exceeded the clinical cut-off of DESR as borderline dysregulation (Biederman, Spencer, et al., 2012; Faraone et al., 2005), while the scores in *Severe general dysregulation* and *Severe dysregulation with high aggressivity* even exceeded the cut-off of Severe DP and those who showed Stringent DP were all from these two severe latent groups as well.

It should be noted that in our investigations, DP is conceptually different from the understanding to be found in the diagnostic classifications of DSM-5 and ICD-11, which treated dysregulation as subtypes of a broader disorder (American Psychiatric Association, 2013; World Health Organization, 2018). In this study, DP is considered as an impairment that exists as associated psychopathology of patient's main diagnosis and presents in parallel with patient's core symptoms. Consequently, the appearance of DP varies in its severity levels and abnormal rates in different clinical groups, and its causal relationship with core symptoms is still unclear. More importantly, the differentiation of latent phenotypes of DP could assist treatment approaches. Treatment should aim to address the large proportion of attentional and behavioural dysregulation mainly in externalizing disorders (ADHD, ADHD+TIC, ADHD+ODD), and the emotionally focused dysregulation mainly in internalizing disorders (depression, anxiety, OCD). In practice, for some clinical groups, such as

TIC or anxiety, DP was not severe to the extent that specific interventions may be needed. In contrast, ADHD-related DP should bring into the more attention due to its severity, frequency, heterogeneity and driving force for comorbidity. Hence, adequate treatment should be decided based on individual's psychopathological profile and psychosocial impairment.

Strengths of this study include the evaluation of DP in a large, diverse clinically referred sample. The comparison between a wide range of categorically 'pure' or comorbid clinical groups, and especially the exploration of heterogeneity with latent structure of DP. The inclusion of five 'pure' and two comorbid clinical groups extended our understanding of how other childhood psychopathologies may be intertwined with the DP (for example, Copeland et al., 2013). However, several *limitations* must also be noted. Our results may be sample dependent and need caution when generalizing to other settings. Children and adolescents in the current study were all patients from the Clinic for Child and Adolescent Psychiatry and Psychotherapy at the University Medical Center of Goettingen, Germany. As a tertiary center. the clinic tends to get referred more serve cases. Moreover, the rate of tic disorders and OCD are over-representative given the clinic is a specialized outpatient center for tic disorders, ADHD and OCD. On the contrary, with the research focus of examining 'pure' clinical groups, disorders usually presented with extensive comorbidity like depression and ADHD are under-representative in our sample. Although these small sample sizes might affect the validity of results in those groups, the examination of characteristics in 'pure' psychopathology acts as the key feature of the present study. The effects of comorbid disorders were considered by limiting to two disorder comorbidity and taking the case of ADHD+ODD and ADHD+TIC. In addition, a 'pure' ODD group could not be obtained due to lack of enough patients fulfilling the stringent selection criteria. Therefore, the effect of the factor ADHD and ODD in the comorbid ADHD+ODD could not be disentangled (in the case of comorbid ADHD+TIC we found an additive effect, since the comorbid group exceeds the severity of solely ADHD or TIC). Further investigations are encouraged to reveal the interplay in this common comorbidity. Lastly, our investigation and findings are cross-sectional due to the limitation of data. Therefore, we were not able to test for longitudinal aspects.

In conclusion, this study provides new evidence into the evaluation of dysregulation profile and its co-existing psychopathologies in children. Specifically, the heterogeneity of DP and its practical meaning could be analyzed. DP widely exists as a transdiagnostic psychopathological factor in clinically referred children in parallel to the core symptoms of their diagnoses, and affects a considerable number of children even when the most stringent criteria are used. Children with comorbid psychopathologies, such as ADHD+ODD and ADHD+TIC, were most affected in both level and abnormal rate. Our findings suggest that during clinical assessment it would be worth to clarify the role of DP-related problems within the general psychosocial impairment of the patient in question. In this respect, the derived latent phenotypes (DP-subgroup-profiles) may not only inform about severity but also about the focus of DP, which would allow a better personalized treatment approach.

ACKNOWLEDGEMENTS

The development of this paper was supported by a scholarship from the Overseas Study Program of Guangzhou Elite Project to B. Wang.

DECLARATION OF INTEREST

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

REFERENCES

Achenbach, T. (1991). Manual for the Child Behavior Checklist/4-18 and 1991 profiles. Burlington, VT: University of Vermont Department of Psychiatry. *Social Development from Infancy to Adolescence*.

Aitken, M., Battaglia, M., Marino, C., Mahendran, N., & Andrade, B. F. (2019). Clinical utility of the CBCL Dysregulation Profile in children with disruptive behavior. *J Affect Disord, 253*, 87-95. doi:10.1016/j.jad.2019.04.034

Althoff, R. R. (2010). Dysregulated children reconsidered. *J Am Acad Child Adolesc Psychiatry, 49*(4), 302-305. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20410722

Althoff, R. R., Rettew, D. C., Ayer, L. A., & Hudziak, J. J. (2010). Cross-informant agreement of the Dysregulation Profile of the Child Behavior Checklist. *Psychiatry Res, 178*(3), 550-555. doi:10.1016/j.psychres.2010.05.002

Althoff, R. R., Rettew, D. C., Faraone, S. V., Boomsma, D. I., & Hudziak, J. J. (2006). Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biol Psychiatry, 60*(9), 903-911. doi:10.1016/j.biopsych.2006.02.025

Althoff, R. R., Verhulst, F. C., Rettew, D. C., Hudziak, J. J., & van der Ende, J. (2010). Adult outcomes of childhood dysregulation: a 14-year follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(11), 1105-1116. e1101.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Ayer, L., Althoff, R., Ivanova, M., Rettew, D., Waxler, E., Sulman, J., & Hudziak, J. (2009). Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. *J Child Psychol Psychiatry, 50*(10), 1291-1300. doi:10.1111/j.1469-7610.2009.02089.x

Bellani, M., Negri, G. A., & Brambilla, P. (2012). The dysregulation profile in children and adolescents: a potential index for major psychopathology? *Epidemiol Psychiatr Sci, 21*(2), 155-159. doi:10.1017/S2045796011000849

Biederman, J., Petty, C., Monuteaux, M. C., Evans, M., Parcell, T., Faraone, S. V., & Wozniak, J. (2009). The CBCL-pediatric bipolar disorder profile predicts a subsequent diagnosis of bipolar disorder and associated impairments in ADHD youth growing up: a longitudinal analysis. *The Journal of clinical psychiatry, 70*(5), 732.

Biederman, J., Petty, C. R., Day, H., Goldin, R. L., Spencer, T., Faraone, S. V., . . . Wozniak, J. (2012). Severity of the aggression/anxiety-depression/attention child behavior checklist profile discriminates between different levels of deficits in emotional regulation in youth with attention-deficit hyperactivity disorder. *J Dev Behav Pediatr, 33*(3), 236-243. doi:10.1097/DBP.0b013e3182475267

Biederman, J., Spencer, T. J., Petty, C., Hyder, L. L., O'Connor, K. B., Surman, C. B., & Faraone, S. V. (2012). Longitudinal course of deficient emotional self-regulation CBCL profile in youth with ADHD: prospective controlled study. *Neuropsychiatr Dis Treat, 8*, 267-276. doi:10.2147/NDT.S29670

Biederman, J., Wozniak, J., Kiely, K., Ablon, S., Faraone, S., Mick, E., . . . Kraus, I. (1995). CBCL clinical scales discriminate prepubertal children with structured interview—derived diagnosis of mania from those with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry, 34*(4), 464-471.

Boomsma, D. I., Rebollo, I., Derks, E. M., Van Beijsterveldt, T. C., Althoff, R. R., Rettew, D. C., & Hudziak, J. J. (2006). Longitudinal stability of the CBCL-juvenile bipolar disorder phenotype: a study in Dutch twins. *Biol Psychiatry, 60*(9), 912-920.

Copeland, W. E., Angold, A., Costello, E. J., & Egger, H. (2013). Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry, 170*(2), 173-179. doi:10.1176/appi.ajp.2012.12010132

De Caluwé, E., Decuyper, M., & De Clercq, B. (2013). The child behavior checklist dysregulation profile predicts adolescent DSM-5 pathological personality traits 4 years later. *Eur Child Adolesc Psychiatry, 22*(7), 401-411.

Deutz, M. H., Geeraerts, S. B., van Baar, A. L., Deković, M., & Prinzie, P. (2016). The Dysregulation Profile in middle childhood and adolescence across reporters: factor structure, measurement invariance, and links with self-harm and suicidal ideation. *Eur Child Adolesc Psychiatry, 25*(4), 431-442.

Döpfner, M., Lehmkuhl, G., Görtz-Dorten, A., Breuer, D., Lehmkuhl, G., & Görtz-Dorten, A. (2008). ***DISYPS-II: Diagnostik-System für psychische Störungen nach ICD-10 und DSM-IV für Kinder und Jugendliche-II*****: Huber: Hogrefe Testverl.**

Faraone, S. V., Althoff, R. R., Hudziak, J. J., Monuteaux, M., & Biederman, J. (2005). The CBCL predicts DSM bipolar disorder in children: a receiver operating characteristic curve analysis. ***Bipolar Disorders, 7*****(6), 518-524.**

Geeraerts, S. B., Deutz, M. H., Dekovic, M., Bunte, T., Schoemaker, K., Espy, K. A., . . . Matthys, W. (2015). The Child Behavior Checklist Dysregulation Profile in Preschool Children: A Broad Dysregulation Syndrome. ***J Am Acad Child Adolesc Psychiatry, 54*****(7), 595-602 e592. doi:10.1016/j.jaac.2015.04.012**

Holtmann, M., Bölte, S., Goth, K., Döpfner, M., Plück, J., Huss, M., . . . Poustka, F. (2007). Prevalence of the Child Behavior Checklist - pediatric bipolar disorder phenotype in a German general population sample. ***Bipolar Disorders, 9*****(8), 895-900.**

Holtmann, M., Buchmann, A. F., Esser, G., Schmidt, M. H., Banaschewski, T., & Laucht, M. (2011). The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. ***J Child Psychol Psychiatry, 52*****(2), 139-147. doi:10.1111/j.1469-7610.2010.02309.x**

Holtmann, M., Goth, K., Wöckel, L., Poustka, F., & Bölte, S. (2008). CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? ***Journal of neural transmission, 115*****(2), 155-161.**

Hudziak, J. J., Althoff, R. R., Derks, E. M., Faraone, S. V., & Boomsma, D. I. (2005). Prevalence and genetic architecture of Child Behavior Checklist–juvenile bipolar disorder. ***Biol Psychiatry, 58*****(7), 562-568.**

Jucksch, V., Salbach-Andrae, H., Lenz, K., Goth, K., Dopfner, M., Poustka, F., . . . Holtmann, M. (2011). Severe affective and behavioural dysregulation is associated with significant psychosocial adversity and impairment. ***J Child Psychol Psychiatry, 52*****(6), 686-695. doi:10.1111/j.1469-7610.2010.02322.x**

Jucksch, V., Salbach-Andrae, H., Lenz, K., Goth, K., Döpfner, M., Poustka, F., . . . Holtmann, M. (2011). Severe affective and behavioural dysregulation is associated with significant psychosocial adversity and impairment. ***J Child Psychol Psychiatry, 52*****(6), 686-695. doi:10.1111/j.1469-7610.2010.02322.x**

Lanza, S. T., & Rhoades, B. L. (2013). Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. ***Prevention Science, 14*****(2), 157-168.**

Masi, G., Muratori, P., Manfredi, A., Pisano, S., & Milone, A. (2015). Child behaviour checklist emotional dysregulation profiles in youth with disruptive behaviour disorders: clinical correlates and treatment implications. ***Psychiatry Res, 225*****(1-2), 191-196. doi:10.1016/j.psychres.2014.11.019**

Masi, G., Pisano, S., Milone, A., & Muratori, P. (2015). Child behavior checklist dysregulation profile in children with disruptive behavior disorders: A longitudinal study. ***J Affect Disord, 186*****, 249-253. doi:10.1016/j.jad.2015.05.069**

Mayes, S., Waxmonsky, J., Calhoun, S., Kokotovich, C., Mathiowetz, C., & Baweja, R. (2015). Disruptive mood dysregulation disorder (DMDD) symptoms in children with autism, ADHD, and neurotypical development and impact of co-occurring ODD, depression, and anxiety. ***Research in autism spectrum disorders, 18*****, 64-72.**

Muthén, L., & Muthén, B. (1998-2015). Mplus Version 7 User's Guide. 1998–2015. ***Statistical analysis with latent variables*****.**

Nobile, M., Bianchi, V., Monzani, D., Beri, S., Bellina, M., Greco, A., . . . Molteni, M. (2016). Effect of family structure and TPH2 G-703T on the stability of dysregulation profile throughout adolescence. ***J Affect Disord, 190*****, 576-584. doi:10.1016/j.jad.2015.10.057**

Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. ***Structural equation modeling, 14*****(4), 535-569.**

Roessner, V., Becker, A., Banaschewski, T., & Rothenberger, A. (2007). Psychopathological profile in children with chronic tic disorder and co-existing ADHD: additive effects. ***Journal of abnormal child psychology, 35*****(1), 79-85.**

Rothenberger, A., & Roessner, V. (2013). The phenomenology of attention-deficit/hyperactivity disorder in Tourette syndrome. In ***Tourette syndrome*** **(pp. 26-49): Oxford University Press, New York.**

Shaw, P., Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion dysregulation in attention deficit hyperactivity disorder. ***Am J Psychiatry, 171*****(3), 276-293. doi:10.1176/appi.ajp.2013.13070966**

van Stralen, J. (2016). Emotional dysregulation in children with attention-deficit/hyperactivity disorder. ***Attention deficit and hyperactivity disorders, 8*****(4), 175-187. doi:10.1007/s12402-016-0199-0**

Volk, H. E., & Todd, R. D. (2007). Does the Child Behavior Checklist Juvenile Bipolar Disorder Phenotype Identify Bipolar Disorder? ***Biol Psychiatry, 62*****(2), 115-120. doi:https://doi.org/10.1016/j.biopsych.2006.05.036**

World Health Organization. (1993). ***The ICD-10 classification of mental and behavioural disorders : diagnostic criteria for research*****.**

World Health Organization. (2018). ***International classification of diseases for mortality and morbidity statistics (11th Revision)*****.**