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Research paper

Sympathetic arousal in children with oppositional defiant disorder and its relation to emotional dysregulation

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A B S T R A C T

Background: Emotional dysregulation (ED) is a trans-nosographical condition characterized by mood instability, severe irritability, aggression, temper outburst, and hyper-arousal. Pathophysiology of emotional dysregulation and its potential biomarkers are an emerging field of interest. A Child Behaviour Checklist (CBCL) profile, defined as Dysregulation Profile (DP), has been correlated to ED in youth. We examined the association between the CBCL-DP and indices of sympathetic arousal in children with Oppositional Defiant Disorder (ODD) and healthy controls.
Method: The current study sought to compare the arousal level measured via electrodermal activity in response to emotional stimuli in three non-overlapping groups of children: (1) ODD + CBCL-DP (n = 28), (2) ODD without CBCL-DP (n = 35), and (3) typically developing controls (n = 25).
Results: Analyses revealed a distinct electrodermal activity profile in the three groups. Specifically, children with ODD + CBCL-DP presented higher levels of sympathetic arousal for anger and sadness stimuli compared to the other two groups.
Limitations: The relatively small sample and the lack of assessing causality limit the generalizability of this study which results need to be replicated in larger, different samples.
Conclusion: The CBCL-DP was associated to higher levels of arousal for negative emotions, consistently with previous reports in individuals with depression and anxiety. Further work may identify potential longitudinal relationships between this profile and clinical outcomes.

1. Introduction

Children with severe dysregulation of emotions and behavior, mood instability, irritability, aggression, temper outburst, and hyperarousal are still a diagnostic challenge in clinical practice, not completely fitting any of the current clinical categories, including Disruptive Behavior Disorders (DBD) or Mood Disorders (MD) (Stringaris and Goodman, 2009). The Child Behavior Checklist (CBCL), one of the most used instruments for assessment of developmental psychopathology (Achenbach and Rescorla, 2004), has been considered a possible tool for identifying children with these features, using the Child Behavior Check List-Dysregulation Profile (CBCL-DP) (Rescorla et al., 2018). Accordingly, the CBCL-DP has become widely regarded as a measure of emotional/behavioral dysregulation (Aitken et al., 2019; Althoff et al., 2012, 2010b,a; Ayer et al., 2009; Holtmann et al., 2011; Kim et al., 2012). Several studies with different populations suggested that the CBCL-DP might be considered as an early developmental trait characterized by impaired self-regulation of affect and behavior leading children to respond emotionally to the environmental stimuli (McQuillan et al., 2018). Overall, it converges with the general factor of psychopathology (Haltigan et al., 2018), and it has been used to identify children at high risk for severe psychopathology (Bellani et al., 2012). Also, it may predict future poor adjustment and negative outcomes, as suicidality or self-harm, substance abuse or personality disorders (De Caluwé et al., 2013; Holtmann et al., 2011). In children with ADHD, the CBCL-DP might predict worse psychosocial functioning, and be associated with clinically significant impairments (Biederman et al., 2018, 2009; Diler et al., 2009; Faraone et al., 2019; Peyre et al., 2015).

Oppositional defiant disorder (ODD) in youth is a strong predictor of mental illness, with a wide range of possible current or developmental associations with other psychiatric disorders (Stringaris and Goodman, 2009). An analysis of prevalent dimensions of ODD shed light on these possible associations, namely the irritable dimension, firstly identified as the only predictor of emotional disorders (Stringaris and Goodman, 2009). Researchers have also demonstrated that irritability as a distinct dimension within ODD symptoms robustly

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predicts depression and anxiety (Burke and Loeber, 2010; Burke, 2012; Burke et al., 2010; Hipwell et al., 2011; Maughan; et al., 2010; Stringaris et al., 2009). Studies also demonstrated that irritability symptoms may distinguish groups of children and that those with irritability are at greater risk for depression and anxiety in adulthood (Burke, 2012; Kuny et al., 2013). Consistently, our previous study found that CBCL-DP score was the only significant predictor of a mood disorder at 14–15 years in a sample of children aged 8 to 9 years with ODD (Masi et al., 2015b). Furthermore, in another sample of youth with ODD, greater CBCL-DP scores were associated to higher levels of autoaggression, even when controlled for the levels of aggression against others and other covariates (Muratori et al., 2017). These findings support the notion that ODD with Emotional Dysregulation may represent a clinical category with peculiar clinical and developmental features, which may more closely be addressed using possible biological markers.

Although growing research described the clinical features of children with high scores on the CBCL-DP worldwide (Rescorla et al., 2018), few studies had examined its biological correlates. A pilot study including a small sample of typical children revealed a significant correlation between glutamate concentrations in the anterior cingulate cortex (ACC), a crucial hub for affect regulation (Stevens et al., 2011), and CBCL-DP score (Wozniak et al., 2012). McGough et al. (2013), using electroencephalography, revealed distinct patterns of underlying neural dysfunction in CBCL/DP that might represent a sort of biosignature of emotional dysregulation. These patterns were similar to those associated with melancholic temperament and depression (Grin-Yatsenko et al., 2009; Robinson, 2001). Finally, Deutz et al. (2018) indicated that elevated levels of heart rate reactivity might be a characteristic in a clinically relevant dysregulated subgroup of children referred for their externalizing behavioral problems.

Electrodermal activity is a well-established noninvasive method to measure the autonomic reactivity, which is a neurobiological correlate of emotion regulation. Differences in the electrical conductance of the skin are measured under the umbrella term of electrodermal activity, which is also known as skin conductance response (SCR). The SCR is often considered as one of the most useful indices of sympathetic arousal because, in comparison to other measurements, such as heart rate, it is not contaminated by parasympathetic activity (Lampinen et al., 2018; Schulte-Mecklenbeck et al., 2011). Therefore, the SCR has been widely used as an index of arousal reactions induced by emotionally evocative stimuli (see for instance, Taskiran et al., 2018), as in the current study.

1.1. The current study

In line with all these findings, our study explored whether children with ODD and CBCL-DP, compared with ODD without CBCL-DP and healthy controls, might be characterized by a specific SCR profile. We hypothesized that the ODD + CBCL-DP group would be associated to higher levels of arousal for stimuli of negative emotions (anger, sadness, and fear), as previously demonstrated in subjects with depression and anxiety (Monk et al., 2001; Smith et al., 2005; Woltering and Shi, 2016). Given the possible clinical and developmental implications of emotional dysregulation in youth with ODD, namely the risk of mood disorders, the identification of possible physiological underpinnings in this specific population with uncertain boundaries may lead clinicians to a timely and focused recognition, and to more specific therapeutic strategies to prevent adverse outcomes.

2. Method

2.1. Participants and procedure

The current study included 88 male participants ranging from 7 to 11 years of age, recruited from a psychiatric hospital and from a community school, both located in Pisa (Italy). Subjects were recruited from January 2018 to December 2018, and they received identical diagnostic, cognitive, and SCR procedures. The inclusion criteria for the clinical sample were: primary diagnosis of ODD, and male gender. The clinical sample included children who were receiving first psychiatry evaluation, and they were free from medication at the moment of this assessment. The subjects in the control sample were gender and age-matched with clinical subjects. Exclusion criteria for all groups included an estimated full-scale intelligence <80, a lifetime history of autism spectrum disorders, and any current history of major depression or panic disorder. The a priori power analysis, using the *Power 3.1.9 (Faul et al., 2007), indicated a sample size of 84 to test our hypothesis (effect size settled at 0.40, p-value fixed at < 0.05, and a power > 0.90).

The sample received a systematic evaluation. Specifically, trained child psychiatrists administered separately to parents and youth a diagnostic clinical interview, the Schedule for Affective Disorders and Schizophrenia for School- Age Children- Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), while parents completed also the CBCL. Cognitive abilities in all participants were assessed with the Wechsler Intelligence Scales for Children – 4th Ed (WISC-IV) (Wechsler et al., 2012).

To the purposes of the current study, using baseline data available on our total sample, we created three non-overlapping groups of subjects: children with ODD and the CBCL-DP (ODD/DP+) ($n = 28$), children with ODD without CBCL-DP (ODD/DP−) ($n = 35$), and a control sample of typically developing children without ODD and without the CBCL-DP ($n = 25$). In the two ODD subsamples, 9 and 8 subjects respectively had ADHD comorbidity. All families were Italian speaking, and all children were Caucasian. All parents and participants provided written permission/assent prior to the initiation of any study. The study conformed to Declaration of Helsinki, and the Ethical Committee of our Hospital approved the study.

2.2. Measures

2.2.1. Categorical diagnosis

Child psychiatrists administered separately to the children and their parents the clinical interview K-SADS PL (Kaufman et al., 1997), which explores the presence or absence of each symptom according to DSM-IV criteria. The mean rate of inter-rater agreement was 0.85 k of Cohen.

2.2.2. Emotional dysregulation

Parents completed the CBCL for each participant (Achenbach and Rescorla, 2004). The CBCL-DP was defined categorically in individuals with the sum of T scores ≥ 210 on the Attention Problems, Aggression, and Anxious/Depressed subscales. Although other approaches have been used to assess the presence/absence of CBCL-DP, the current approach has received increasing support. In fact, several studies supported its factorial structure, gender invariance, reliability and clinical utility (Deutz et al., 2016; Geeraerts et al., 2015; Haltigan et al., 2018; Joshi et al., 2018; Uchida et al., 2014). In the current sample, the reliability coefficients (Cronbach) of CBCL Attention Problems, Aggression, and Anxious/Depressed subscales were: 0.82, 0.81 and 0.82, respectively.

2.2.3. Intellectual functioning

Cognitive abilities were assessed with the Wechsler Intelligence Scales for Children – 4th Ed. (Wechsler et al., 2012). We reported the mean of total score of IQ for each group in Table 1.

2.2.4. Skin conductance response

Sympathetic arousal was assessed by electrodermal activity signal, which has been obtained with the aid of the minimally obtrusive wireless sensor Shimmer3 GSR+ Unit by Shimmer Sensing, Inc. (Dublin, Ireland). The Shimmer GSR+ monitored skin conductivity

Table 1
Characteristics of the samples.

	ODD/DP + *N* = 28	ODD/DP-*N* = 35	TD *N* = 25	*F* o χ^2	*p*
Age, y	9.04 (0.97)	9.34 (1.18)	9.00 (1.53)	*F* = 0.210	NS
CBCL TOT	70.19 (4.17)	63.86 (3.13)	54.61 (2.19)	*F* = 108.86	.000
IQ WISC IV	101.38 (6.50)	101.50 (7.75)	101.83 (5.96)	*F* = 0.021	NS
Family income, euros	17.450 (1.77)	18.780 (1.89)	19.310 (1.50)	*F* = 0.788	NS
ADHD comorbidity, *N*	8	9	_	$\chi^{2=0}$.064	NS

Notes. CBCL TOT: Child Behavior Checklist Total Problems; IQ WISC IV: Wechsler Intelligence Scale for Children Fourth Edition full scale Intelligence Quotient; ADHD comorbidity comparison was conducted only for the clinical samples. ODD/DP + group has CBCL TOT score higher than ODD/DP- group ($p < .05$) and than TD group ($p < .00$); ODD/DP- group has CBCL TOT score higher than TD group ($p < .01$).

between two reusable electrodes attached to two fingers of the child's non-dominant hand. The acquisition-sampling rate, according to the specifications of the manufacturer, was 51.2 Hz. Electrodermal activity has been recorded while children were comfortably sat on a chair and were presented with emotionally salient stimuli on a 22-inch flat screen monitor. The stimuli were images from the *NimStim Set of Facial Expressions* (Tottenham et al., 2009), which consisted of naturally posed photographs of professional actors. Actors were instructed to make different facial expressions. We selected imaging depicting happy, sad, angry, fearful, disgusted expressions. We used photographs of 4 actors, 2 males and 2 females. The authors of this set of images tested the percentage of emotion recognition for each expression (Tottenham et al., 2009). The faces were presented on a black background. Subjects were presented with 24 images (4 actors, each displaying 6 emotional expressions). Each stimulus was presented individually for 4 s and the order of the stimuli was randomized across actors and emotions. The stimuli were interspersed with grey crosses on a black background lasting 20 s. The electrodermal activity signal analysis was performed using the MATLAB (v. R2018a, The MathWorks, Inc., Natick, MA, USA)-based Ledalab software v.3.4.9 (Benedek and Kaernbach, 2010). Changes in SCR were determined by subtracting the activity in the 1 s before the photograph started to be shown from that occurring during the presentation of the photograph. More specifically, the SCR was scored as the largest increase in conductance between 1 and 6 s after the beginning of the photograph presentation compared to the mean activity in a 1s pre-stimulus baseline interval (Wieser et al., 2009).

3. Data analysis

Statistical tests were run in SPSS 21.0. Since there were significant differences in the means of the total problem score of the CBCL among groups, the CBCL total score was used as a covariate in all analyses. Separate univariate analyses of variance with covariates (ANCOVAs) were conducted using group as the independent variable, the SCR to the various stimuli as dependent variables, and the CBCL total score as covariate. Post-hoc comparisons (Tukey test) were used when the univariate ANCOVAs were significant ($p < .05$) to determine pairwise differences between groups. The data that support the findings of this study are available from the corresponding author upon reasonable request.

4. Results

Table 1 shows the characteristics of the three groups of children. The groups did not differ in age, IQ and income, but the ODD/DP + group reported higher values in the total score of the CBCL than the other two groups. The ODD/DP + group scored significantly higher on other CBCL total score compared to ODD/DP- group, while both of these had significantly higher CBCL total scores than controls (all differences $p < .05$).

Analyses revealed a distinct SCR profile in ODD/DP + participants compared with controls or ODD/DP − (see Figs. 1 and 2). Specifically, the groups exhibited differences in SCR to anger ($F = 5.16$; $p = .008$) and SCR to sadness ($F = 6.36$; $p = .003$). Post-hoc pairwise comparisons indicated that, for both emotions, the ODD/DP + was significantly more aroused than the ODD/DP- and the control group ($p < .01$), whereas there were no differences in SCR to anger and SCR to sadness profiles between ODD/DP- and control group. No differences emerged among groups when we used SCR to the other emotional stimuli as dependent variables.

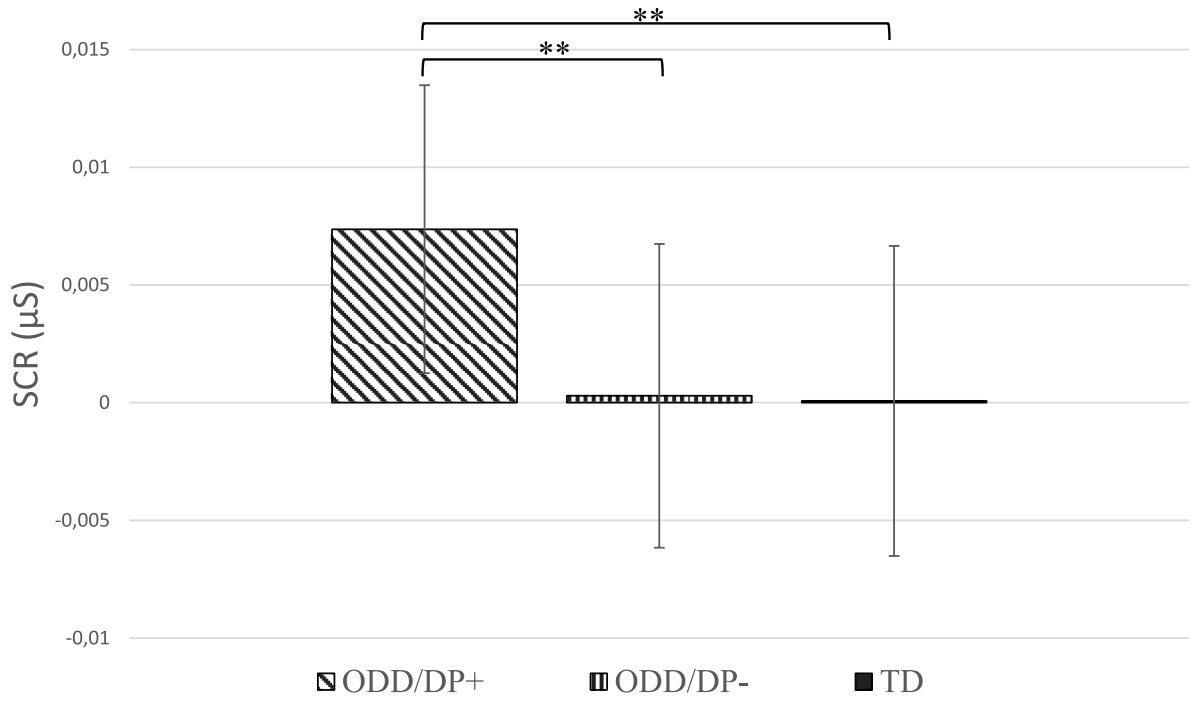
5. Discussion

In this study, we examined the SCR profile, a marker of sympathetic arousal, in relation to the CBCL-DP, in a sample of 7 to 11-year old children with ODD. Our results suggested that the ODD/DP + group has a unique profile characterized by a higher sympathetic arousal for anger and sadness stimuli that differentiates it from both the ODD/DP- and the typical children groups. This finding suggests that the CBCL-DP could identify ODD patients with specific biological profiles that are distinct from ODD alone. In this context, it is relevant that our results were controlled for the possible confounder of the global levels of behavioral problems, as measured by the CBCL total problem score.

Recently, we pointed out the importance of assessing the CBCL-DP in ODD patients, likely to be a key feature in their psychopathology (Masi et al., 2015a), and an early marker for subsequent mood disorder (Masi et al., 2015b). An association between CBCL-DP and the risk of later mood disorders has been also found in at-risk populations (for a review about CBCL-DP and adult psychopathology, see Bellani et al., 2012). For instance, Meyer et al. (2009), in a 23-year longitudinal study conducted on a sample of 101 youths at risk for major mood disorders, found that children with the CBCL-DP were more likely to develop severe psychiatric symptoms, including emotional comorbidities and bipolar disorder in young adulthood. Similarly, in a sample of 325 children, higher CBCL-DP scores during childhood were associated with increased rates of mood disorders and suicidality 19 years later (Holtmann et al., 2011). Finally, Biederman et al. (2013) reported comparable relations in an ADHD sample.

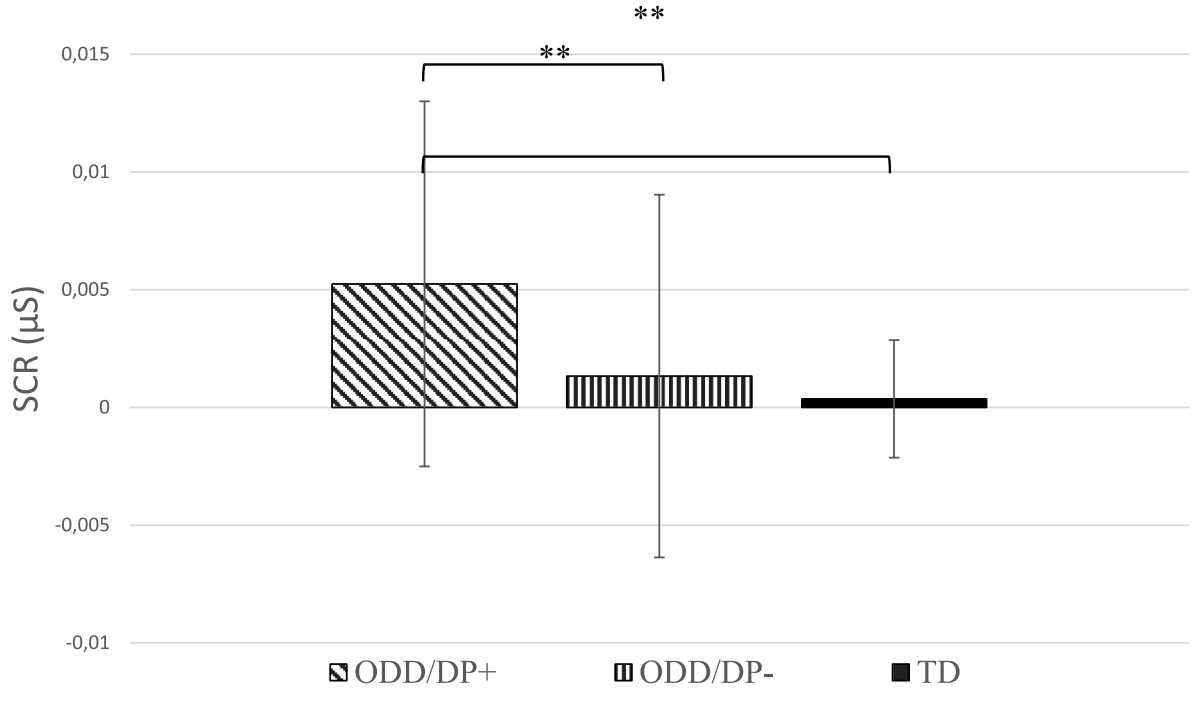
In line with these findings, our ODD/CBCL + DP group was characterized by elevated levels of arousal for negative emotions (anger and sadness), as has been consistently demonstrated with depression and anxiety (Monk et al., 2001; Smith et al., 2005; Woltering and Shi, 2016). Furthermore, sympathetic over-arousal has been associated with internalizing symptoms in children with externalizing behaviors (Fanti, 2018; Scarpa et al., 2010; Schoorl et al., 2016), and has been suggested to explain the co-occurrence between aggression and anxiety (Bubier and Drabick, 2009).

In the present study, none of the ODD children had full criteria for mood or anxiety disorders diagnosis, but, given the high arousal, we could hypothesize an increased risk for comorbid anxiety/depression, supporting the prognostic value of CBCL-DP across spectra (Maughan et al., 2004). Because of its empirical nature, its excellent psychometric properties, and its ease of use as a paper and pencil instrument, the DP of the CBCL may be a reliable measure for the identification of children with these characteristics, especially in routine



Notes. ** $p < .001$

Fig. 1. SCR for angry faces.
Notes. **$p < .001$.



Notes. ** $p < .001$

Fig. 2. SCR for sad faces.
Notes. **$p < .001$.

care services.

Our study did not find SCR differences between ODD/DP− and control groups. In other words, ODD/DP+ had a unique signature, whereas ODD alone did not have.

Importantly, the autonomic response to emotional stimuli is regulated by the sympathetic and parasympathetic nervous systems which operate synergically. According to the "fight-or-flight" response, the response to a stressful stimulus is marked by physical changes, including nervous and endocrine changes, that prepare a human or an animal to react or to retreat. In particular, the "fight" behavior is correlated by activation of the sympathetic nervous system while the "flight" response is mainly linked to parasympathetic activation. Notably, during the reaction, the intensity of emotion that is brought on by the stimulus also determine the nature and intensity of the behavioral response (Kop et al., 2011). While an excessive "fight" response may be manifested in angry or argumentative behavior; an excessive "flight" response may be manifested through social withdrawal or substance abuse. In the context of the "fight-or-flight" response, emotional regulation is used proactively to avoid threats of stress or to control the level of emotional arousal. Thus, individuals with emotional dysregulation may be prone to anxiety and aggression. Our results of increased SCR in ODD/DP+ compared to healthy controls and ODD/DP- could suggest an imbalance of the "fight-or-flight" response towards an increased level of sympathetic activation in this specific subgroup, which may due to an impairment in emotional regulation. If, confirmed, this finding suggests that the dysregulated dimension of the ODD may present a clear bio-correlate as seen in recent articles on SCR on cognitively normal subjects (Wang et al., 2018) and psychiatric patients (Ameller et al., 2017). Further studies disentangling ODD samples for other dimensions (e.g. headstrong and hurtful), as well as for clinical severity, may help to further explore other possible biological specificities.

The use of tools for the monitoring of physiological signals is of outstanding importance in psychiatry. Indeed, these systems may be able to acquire objective measures to identify symptoms associated with the specific disorder. In particular, SCR is one of the most frequently used methods in psychophysiology for the assessment of sympathetic responses (Fontanella et al., 2012), due to fairly simple methodology, ease of measurement, and high re-test reliability. Importantly, wireless technologies provide the opportunity to easily achieve the monitoring of such signals in a non-intrusive way; therefore, they are particularly relevant for young patients who may be less compliant to conventional monitoring techniques (Crifaci et al., 2013; Di Palma et al., 2017). Despite the great advantages that wearable solutions could provide if used in clinical routine, they are still mainly applied in dedicated programmes and at the pilot level. Barriers of implementation of wearable technologies in healthcare systems are mainly due to the structure and care delivery models of the healthcare system, and from the immaturity of the technological solutions existing today (Lewy, 2015). As far as the healthcare system is concerned, today it is commonly dispersed, not allowing sharing of information and care. Since wearable technologies aim to provide information that integrates data from different sources, complement the clinical data and generate new knowledge, implementing these technologies will require changing the model of delivery of care from a fragmented delivery focusing on disease-specific care to new more inclusive models of care. In particular, intervention modalities of care should consider the individual's preferences and needs, and provide data to all care providers such as behavioral, functional and mental information. From a technological point of view, a barrier in the application of wearable systems in clinical routine consists in the fact that they usually require additional time, education and training to be used, thus increasing the workload and cost for organizations. For this reason, it is important to implement technologies that are easy to use by the healthcare professional and that can be implemented as part of the best practice and workflow to enhance adoption by the care providers. Finally, it is necessary that the wearable devices consider standardization, privacy and security issues, and interoperability to be applied in clinical routine.

The study has several limitations. Although well selected, the findings were based on a relatively small number of participants. The relations of SCR findings to the CBCL-DP require confirmation in larger samples that include female subjects, broader age ranges and children with other psychiatric diagnoses. Larger clinical samples would also offer the opportunity to identify additional subtypes of ODD, with sympathetic arousal correlates potentially different from CBCL-DP profiles. Furthermore, causality cannot be determined from this study, since our findings are exploratory rather than explanatory, and replication in different samples is needed. However, it seemed that altered arousal predicts subsequent psychiatric problems rather than vice versa (Latvala et al., 2016; Portnoy and Farrington, 2015). Finally, in youth with conduct problems, also the presence of high Callous Unemotional (CU) traits has been considered an important clinical dimension with specific prognostic implications (Frick et al., 2014). Similarly, to the presence of CBCL-DP, also CU traits identify a subgroup of individuals with distinctive neurocognitive characteristics (Pisano et al., 2017). Theoretically, children with high levels of CU traits show and persist in behavioral problems due to emotional hypoactivity, whereas children with CBCL-DP do so due to their emotional hyperactivation. Unfortunately, the small sample size did not permit us to test this hypothesis in the current study.

6. Conclusions

Some clinical implications of these findings can be proposed. Firstly, our findings add evidences to the CBCL-DP as a cross-disorder dimensional measure of psychopathology with specific biological correlates. Secondly, our findings indicate that a clinical index (CBCL-DP) is associated with increased emotional reactivity, and might be characteristic for a clinically relevant subgroup of ODD children. Further studies are needed for a better validation of these findings in other clinical populations with different categorical diagnoses, in order to better specify the respective roles of the emotional dysregulation and of the psychiatric diagnosis. However, if confirmed, these findings on the role of SCR may ultimately help timely and reliable diagnoses, as well as focused treatment strategies for specific subgroups of patients. Further studies should explore whether the identified SCR profiles for ODD/DP + may represent a possible predictor for treatment response, or a moderator of clinical outcomes, in children with behavioral problems (Masi et al., 2016). An integration of behavioral and brain-based objective approaches in clinical decision-making is a new window of opportunity for improving our diagnostic, preventative and therapeutic possibilities for emotional and behavioral problems in children.

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Conflict of interest

Dr. Masi was in advisory boards for Eli Lilly, Shire and Angelini, has received research grants from Eli Lilly, Shire and Lundbeck, and has been speaker for Eli Lilly, Shire, Lundbeck, Otsuka, and FB Health. None of the other authors has any conflict of interest related to this manuscript.

CRediT authorship contribution statement

Alessandro Tonacci: Writing - original draft, Formal analysis, Writing - review & editing. **Lucia Billeci:** Writing - original draft,

Conceptualization, Writing - review & editing. **Sara Calderoni:** Methodology, Writing - review & editing. **Valentina Levantini:** Data curation, Writing - review & editing. **Gabriele Masi:** Methodology, Writing - review & editing. **Annarita Milone:** Methodology, Writing - review & editing. **Simone Pisano:** Methodology, Writing - review & editing. **Pietro Muratori:** Writing - original draft, Conceptualization, Writing - review & editing.

Data for reference

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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