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Emotional dysregulation and callous unemotional traits as possible predictors of short-term response to methylphenidate monotherapy in drug-naïve youth with ADHD

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ABSTRACT

Background: Emotional dysregulation (ED) and callous unemotional (CU) traits can be associated with ADHD in youth, influencing its natural history and outcome, but their effect on medication efficacy is unexplored. We examined whether two measures of baseline ED and CU traits, the Child Behavior Checklist-Dysregulation Profile (CBCL-DP) and the Antisocial Process Screening Device (APSD), respectively, were predictors of change of ADHD-Rating Scale (ADHD-RS) after a 4-week methylphenidate (MPH) monotherapy.
Methods: 43 patients (37 males, 8–16 years, mean 9.9 ± 2.7 years) were included. Hierarchical linear regression models were used to explore whether CBCL-DP and APSD might predict ADHD-RS score, controlling for baseline severity.
Results: Baseline CBCL-DP predicted higher post-treatment ADHD-RS scores in total and hyperactivity-impulsivity, but not in inattention subscale. Baseline APSD was not significantly related to ADHD-RS scores at the follow-up.
Limitations: Small sample size, lack of gender diversity, non-blind design and short period of observation.
Conclusion: ED, assessed with that CBCL-DP, might be a negative predictor of change of hyperactive-impulsive symptoms after MPH treatment and should be systematically assessed at baseline.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with persistent inattention and/or hyperactivity/impulsivity, present in at least two life contexts, associated with significant social and academic impairment and with onset before 12 years of age [1]. Oppositional Defiant Disorder (ODD) frequently co-occurs with ADHD, particularly in those with combined presentation (both inattention and hyperactivity/impulsivity) [2].

About 24 to 50% of youth and 34 to 70% of adults with ADHD have been reported with an associated emotional dysregulation (ED) [3], that is, an impaired regulation of emotional states, excessive and inappropriate emotional expressions, high excitability and lability, temper outbursts, low tolerance to frustration, and slow return to baseline [3–5]. These emotional and behavioral features are more frequent in the combined presentation of ADHD, and their severity increases with the severity of ADHD symptoms, further worsening functional impairment, social adjustment, and peer-relationships [6,7], and leading to more frequent need for interventions [8].

The challenging exploration of the affective and behavioral components of ED has been variously addressed. The Child Behavior Checklist (CBCL) [9], a widely used measure for developmental psychopathology, is a possible tool for identifying children with ED, using an elevation in 3 syndrome scales (Anxiety/Depression, Aggression, Attention) [10]. This profile, called CBCL-Dysregulation Profile (CBCL-DP), has been principally explored in youth with ADHD, defining a subgroup with a more severe clinical picture, poorer prognosis, and different developmental trajectories [11–13]. The scores of CBCL-DP are positively associated also with objective indices of ED [14]; however, it should be stressed that they cannot be considered an equivalent of the wider concept of ED.

While ED has been largely explored in youth with ADHD [4], less evidence is available on Callous-Unemotional (CU) traits in ADHD. The CU traits are characterized by a persistent disregard for others, and a lack of empathy and generally deficient affect. Among the different measures to assess CU traits [15], the Antisocial Process Screening Device - APSD [16], parent version, has been used to assess children and adolescents

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[17]. CU traits are associated with higher risk of conduct problems [18,19], persisting disruptive and antisocial behavior over time [20,21], and poorer response to behavioral interventions [22–24].

Intervention in children with ADHD and significant impairment should be multimodal, and include both medications and behavioral treatments [25,26]. Psychostimulants, both methylphenidate (MPH) and amphetamines, are the first pharmacological option [27]. In a recent clinical study on 518 Spanish youth, possible negative predictors of efficacy of stimulants were ADHD severity, lower IQ, comorbidities (namely, ODD, depression, substance use disorder), and lower scores in neuropsychological testing as significant variables (including commission errors in the Continuous Performance Test) [28].

Although both ED and CU can influence natural history and outcome of ADHD and comorbid conditions, their role on the short-term pharmacological treatment response is less clear. In this study, we examined if ED, assessed with the CBCL-DP, and CU traits, assessed with the APSD, can affect the response to MPH in children with ADHD with and without ODD. We hypothesized that both CBCL-DP and APSD may predict the severity of ADHD symptoms at a follow-up after MPH treatment in hyperactive/impulsive and inattentive domains.

2. Method

2.1. Sample

A consecutive sample of 43 Caucasian children and adolescents was recruited from January to December 2018 in the ADHD Section of our Hospital. The sample included 37 male and 6 females, aged between 8 and 16 years (mean age 9.93 ± 2.71 years), with a mean of IQ of 92.73 ± 12.10. Twelve (28%) participants were also diagnosed with ODD, no other psychiatric comorbidities were reported. The inclusion criteria were: 1) main diagnosis of ADHD according to the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version - K-SADS-PL [29] and DSM-5 [1] diagnostic criteria; 2) a Full Scale IQ (WISC-IV) of 80 or above; 3) caregivers consent to pharmacological treatment. Exclusion criteria were an estimated Full-Scale IQ < 80 and any pharmacological treatment at the baseline.

All participants and parents were informed about assessment instruments and treatment options. Written informed consent was obtained from parents as well as from children 7 years and above. The study conformed to Declaration of Helsinki; the Ethical Committee of our Hospital approved the study.

2.2. Measures

Categorical diagnosis: A semi-structured interview, the K-SADS-PL, was separately administered by trained child psychiatrists to parent(s) and youth. The mean inter-rater agreement was 0.85 (Cohen's Kappa).

Emotional dysregulation: Parents completed the CBCL for each participant. The CBCL-Dysregulation Profile (DP) was computed by summing the T-scores of three CBCL subscales: Attention Problems, Aggression and Anxious/Depressed. CBCL-DP factorial structure, gender invariance and reliability have been already explored [30–33]. In our study, the reliability coefficients (Cronbach's Alpha) of CBCL Attention Problems, Aggression and Anxious/Depressed subscales were respectively, 0.82, 0.81 and 0.82.

Intellectual functioning: Intelligence was assessed with the Italian version of the Wechsler Intelligence Scales for Children – 4th Ed. [34].

Callous-Unemotional traits: The Antisocial Process Screening Device – APSD [16], parent version, was used to evaluate CU traits. This measure includes items for narcissism (7), CU traits (6), and impulsivity (5), rated according to a 3-point Likert scale, Not At All True (0), Sometimes True (1) or Definitely True (2). In our study, internal consistency (Cronbach's Alpha) for the CU traits was 0.81.

ADHD severity: The ADHD Rating Scale-IV [45], an 18-item questionnaire, completed by the parent(s), measures ADHD symptoms according to the DSM-5. The ADHD-RS consists of two subscales: Inattention (IA, 9 items) and Hyperactivity-Impulsivity (HI, 9 items). Parents completed the ADHD-RS both at baseline and after 4 weeks of MPH treatment.

2.3. Treatments and monitoring

All 43 patients were drug-naïve at baseline and were treated in monotherapy during the follow-up. At the baseline (*T*0), patients received a dose-test of MPH Immediate Release (5 or 10 mg, according to age and weight). After one week, the MPH starting dose was increased, with successive titrations of 5–10 mg, twice a day (8 am and 2 pm), no more frequently than at 5-day intervals, with flexible titration, based on age, weight, clinical response and side effects, with weekly monitoring visits. After 4 weeks (*T*1), MPH dosage was 5–30 mg/day (mean dose 15.2 ± 7.42 mg/day, or 0.46 mg/kg/day), with further increases during the follow-up.

2.4. Statistical analysis

We determined the sample size using a priori power analysis, *Power 3.1.9 [35]. To test our hypothesis, we needed a sample size of 43 subjects, for an effect size settled at 0.45, a level of significance for a p-value < .05, and a power > 0.90. We used three hierarchical linear regression models with two blocks. In the first model, the dependent variable was the ADHD-RS Total Score after 4 weeks of treatment. Age, gender, ADHD-RS Total Score at baseline (block 1) and CBCL-DP score as well as CU levels at baseline (block 2) were predictors. In the second model, the dependent variable was the score on the ADHD-RS HI scale after 4 weeks of treatment. Age, gender, ADHD-RS HI, ADHD-RS IA scale at baseline (block 1) and CBCL-DP score as well as CU levels at baseline (block 2) were predictors. In the third model, the dependent variable was the score on the ADHD-RS IA scale after 4 weeks of treatment. Age, gender, ADHD-RS IA, ADHD-RS HI scales at baseline (block 1) and CBCL-DP score as well as CU levels at baseline (block 2) were predictors.

All statistical analyses were conducted with the Statistical Package for Social Science (SPSS Inc.), version 24. A probability level of $p < .05$ indicated statistical significance.

3. Results

Table 1 shows variables' means and correlations among variables. Correlations indicated that the CBCL-DP scores were significantly related with all ADHD severity scores at the baseline and follow-up, whereas the levels of CU traits were significantly related with inattention severity at baseline only. The ADHD-RS total scores decreased from 34.12 (sd = 9.68) to 19.49 (sd = 8.72) during MPH treatment. Based on an improvement of ADHD-RS of at least 30% (partial responders) and 50% (responders), 14 (32.5%) patients were partial responders, and 20 (46.5%) patients responders at the fourth week.

Table 2 shows the linear regression model predicting ADHD-RS, Total Score after 4 weeks of treatment. The tested model explained around 40% of the variance. A significant effect of CBCL-DP emerged, even after controlling for the effects of the ADHD-RS Total Score at baseline. Thus, higher levels of CBCL-DP at baseline assessment predicted higher levels of overall symptoms of ADHD at follow-up. The levels of children's CU traits were not significantly related to the total score of ADHD-RS at follow-up. The mean Variance Inflation Factor (VIM) of 1.1 indicated no multicollinearity in this model.

Table 1
Correlations between variables.

	ADHD-RS(T0)	ADHD-HI(T0)	ADHD-IA(T0)	ADHD-RS(T1)	ADHD-HI(T1)	ADHD-IA(T1)	CU	DP	Age
ADHD-RS(T0)									
ADHD-HI(T0)	0.866**								
ADHD-IA(T0)	0.821**	0.428**							
ADHD-RS(T1)	0.604**	0.512**	0.493**						
ADHD-HI(T1)	0.614**	0.635**	0.375*	0.919**					
ADHD-IA(T1)	0.488**	0.295	0.530**	0.911**	0.675**				
CU	0.249	0.094	0.354*	0.109	0.111	0.087			
DP	0.627**	0.653**	0.390**	0.533**	0.603**	0.367*	0.126		
Age	−0.128	−0.239	0.038	−0.057	−0.019	−0.088	0.036	−0.116	
Gender	0.045	−0.010	−0.031	0.078	0.010	0.107	−0.010	−0.128	−0.040
Means (SD)	34.12 (9.68)	15.84 (6.03)	18.23 (5.29)	19.49 (8.72)	9.21 (4.87)	10.28 (4.65)	4.72 (2.13)	204.16 (19.08)	9.93 (2.71)

Notes: ADHD-RS(T0) = Total Score on the ADHD-RS at the baseline; ADHD-HI(T0) = Score on the ADHD-RS Hyperactivity-Impulsivity subscale (HI) at the baseline; ADHD-IA(T0) = Score on the ADHD-RS Inattentive subscale (IA) at the baseline; ADHD-RS(T1) = Total Score on the ADHD-RS at follow-up; ADHD-HI(T1) = Score on the ADHD-RS HI subscale at follow-up; ADHD-IA(T1) = Score on the ADHD-RS IA subscale at follow-up; CU = callous unemotional; DP = Dysregulation Profile; Age = age at the baseline; Gender = 2 female.
Values are unstandardized estimates.
* $p < .05$.
** $p < .01$.

Table 3 reports the linear regression model predicting ADHD-RS HI scale at follow-up. The tested model explains a significant part of the outcome variance, around 50%, with a relevant role of the CBCL-DP scores at baseline; higher levels of DP at baseline assessment predicted higher levels of hyperactive symptoms of ADHD at follow-up, even after controlling for the effects of the ADHD-RS HI and ADHD-RS IA scales at baseline assessment. The levels of children's CU traits were not related to the score of HI scale of the ADHD-RS at follow-up. The mean VIF of 1.2 indicated no multicollinearity in this model.

The model that tested ADHD-RS IA scores at follow-up as a dependent variable (see Table 4) explained around 35% of the outcome variance, the model did not find any significant relations between the levels of CBCL-DP and CU traits at baseline, only the levels of the ADHD-RS IA at baseline predicted the levels of the ADHD-RS IA score at follow-up. The mean VIF of 1.2 indicated no multicollinearity in this model.

Table 2
Hierarchical linear regression model predicting ADHD total score after 4-weeks of treatment.

	B	SD	p	B	SD	p
ADHD-RS(T0)	0.55	0.11	.00	0.41	0.15	.01
Age	0.08	0.41	.83	0.12	0.41	.76
Gender	0.85	0.16	.37	0.39	0.13	.28
R^2	0.37					

	B	SD	p
CU	0.16	0.53	.76
DP	0.13	0.07	.04
R^2	0.43		

Notes: ADHD-RS(T0) = Total Score on the ADHD-RS at the baseline; CU = callous unemotional; DP = Dysregulation Profile; SD = standard deviation.

Table 3
Hierarchical linear regression model predicting ADHD hyperactivity scores after 4-weeks of treatment.

	Block 1			Block 2		
	B	SD	p	B	SD	p
ADHD-HI(T0)	0.51	0.11	.00	0.36	0.13	.01
ADHD-IA(T0)	0.09	0.13	.45	0.05	0.13	.68
Age	0.24	0.23	.31	0.23	0.22	.32
Gender	0.11	0.69	.50	0.43	0.66	.39
R^2	0.44					

	Block 2		
	B	SD	p
CU	0.01	0.29	.96
DP	0.10	0.04	.04
R^2	0.50		

Notes: ADHD-HI(T0) = Score on the ADHD-RS Hyperactivity-Impulsivity subscale at baseline; ADHD-IA(T0) = Score on the ADHD-RS Inattentive; CU = callous unemotional; DP = Dysregulation Profile; SD = standard deviation.

4. Discussion

This study was aimed at exploring whether CBCL-DP and the APSD baseline scores may predict the severity of ADHD symptoms at follow-up after a 4-week MPH treatment in the two ADHD domains (i.e., hyperactivity/impulsivity and inattention), separately, and in combination (total score of the ADHD-RS). Our findings show a significant effect of CBCL-DP on MPH response, according to the ADHD-RS. Higher levels of CBCL-DP at the baseline assessment predicted higher levels of overall symptoms of ADHD at follow-up. Furthermore, higher levels of CBCL-DP at baseline assessment predicted higher levels of hyperactive/impulsivity symptoms of ADHD at follow-up. By contrast, baseline APSD scores did not influence the MPH response.

Table 4
Hierarchical linear regression model predicting ADHD inattentive scores after 4-weeks of treatment.

	Block 1			Block 2		
	B	SD	p	B	SD	p
ADHD-HI(T0)	0.05	0.12	.66	0.06	0.13	.68
ADHD-IA(T0)	0.45	0.13	.00	0.46	0.12	.00
Age	0.15	0.24	.55	0.15	0.23	.52
Gender	0.67	0.80	.36	0.86	0.79	.30
R^2	0.31					

	Block 2		
	B	SD	p
CU	0.25	0.31	.43
DP	0.06	0.04	.19
R^2	0.35		

Notes: ADHD-HI(T0) = Score on the ADHD-RS Hyperactivity-Impulsivity subscale at baseline; ADHD-IA(T0) = Score on the ADHD-RS Inattentive; CU = callous unemotional; DP = Dysregulation Profile; SD = standard deviation.

It is noteworthy that CU traits, assessed with the APSD, failed to predict ADHD symptoms severity at follow-up, after MPH treatment. Previous findings indicate that youths with disruptive behavior disorders and elevated CU traits display a poorer response to non-pharmacological interventions [21–23]. However, pretreatment CU traits did not predict worse outcome in aggressive children with ADHD receiving a stimulant pharmacotherapy [36].

Our findings indicate a stronger relationship between CU traits and ODD/CD symptoms rather than on ADHD symptoms. This may be accounted for by different neurobiological bases of ADHD versus ODD/CD symptoms (for a review of possible markers of CU in the Central Nervous System, see [37]). In ADHD children, the CU traits are mostly related to lower moral regulation and low empathy, independently to the levels of ADHD symptoms [38]. Irrespective to its role as predictor of pharmacological response, CU traits represent a helpful diagnostic tool for ascertaining a subgroups of severe patients with specific developmental trajectories and therapeutic needs [20].

Regarding the meaning of the CBCL-DP, it explores only some of the possible aspects of the complex concept of ED. CBCL-DP was firstly related to the bipolar spectrum [11], although this relationship has not been confirmed by others [39]. More likely, it may represent a risk marker of a complex self-regulation disorder, with early-onset, including both internalizing and externalizing features, in association with other different disorders (particularly ADHD), giving rise to personality traits and symptoms, predictive of later dysregulation of affects and behavior persisting up to young adulthood [13,40,41].

The effects of baseline CBCL-DP on MPH response may be interpreted as a consequence of a worsening of the affective balance after stimulants. However, previous studies suggest that, psychostimulants may improve emotional lability in patients with ADHD [42,46]. A meta-analysis on adult ADHD patients, including 21 trials, [5], explored the efficacy of pharmacological treatments of ADHD (stimulants and atomoxetine) on ED. The study showed that medications can improve not only core symptoms of ADHD, but also ED, although with a smaller effect size (SMD = 0.34, 95% CI = 0.23–0.45), compared to that reported for the ADHD symptoms (0.80) [27].

An alternative hypothesis may be that ADHD associated with CBCL-DP represents a more severe and treatment resistant subtype of ADHD. This hypothesis is confirmed by the positive correlation between CBCL-DP scores and all ADHD severity scores, both at baseline and at follow-up. Clinical, neuroimaging and genetic studies support the notion that ED may be considered an additional component of ADHD symptomatology, and its role should be considered when diagnostic criteria are revised [4,43]. However, a reliable and comprehensive measure of ED, in its multiple components, in both youth and adults, is still lacking, and this issue represents a major constraint for studies on ED in psychiatric populations.

Pathophysiological bases of ED in ADHD are still unclear. According to the "dyscontrol hypothesis" [44], ED may be one of the possible manifestations of executive function deficits in top-down inhibitory processes, with impaired emotional regulation, while emotional processing may be normal. According to an "affectivity hypothesis", the emotional processing per se may be abnormal, based on bottom-up circuits dysfunctions (amygdala, orbitofrontal cortex, and ventral striatum), underpinning processing of emotional stimuli. Stimulants, mostly effective on core symptoms of ADHD, through modulation of fronto-parietal circuits, may be less effective on the bottom-up circuits related to the ED [5], accounting for a poorer response to treatment.

Major limitations of the study are the small sample size, the lack of gender diversity (only six females were included), the non-blind design and the short period of observation. Furthermore, according to the ADHD-RS score and the rate of comorbidity, these patients were only moderately severe, and treated with relatively low doses of medication, limiting the generalization of the findings. Another limitation is the parent-report treatment bias (i.e., parents report a clinical improvement because the treatment has started). However, our results indicate that CBCL-DP is a significant negative predictor of response to the treatment with MPH, and this measure should be a component of the assessment procedure, helpful for planning timely and finely customized treatment strategies.

Declaration of competing interest

Dr. Masi was in advisory boards for Angelini, received grants from Lundbeck and Humana, and was speaker for Angelini, FB Health, Janssen, Lundbeck, and Otsuka. Dr. Cortese declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) for lectures delivered for ACAMH, and from the Healthcare Convention for Educational Activity on ADHD. The other authors report no other conflicts of interest.

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