A Potential Electroencephalography and Cognitive Biosignature for the Child Behavior Checklist–Dysregulation Profile

James J. McGough, M.D., James T. McCracken, M.D., Alexander L. Cho, B.S., Edward Castelo, B.A., Alexandra Sturm, B.S., Jennifer Cowen, Ph.D., John Piacentini, Ph.D., Sandra K. Loo, Ph.D.

Objective: The Child Behavior Checklist–Dysregulation Profile (CBCL/DP) identifies youth at increased risk for significant psychopathology. Although the genetic architecture and several biological correlates of the CBCL/DP have been described, little work has elucidated its underlying neurobiology. We examined the potential utility of electroencephalography (EEG), along with behavioral and cognitive assessments, in differentiating individuals based on the CBCL/DP. **Method:** Participants aged 7 to 14 years of age were categorized into 3 age- and sex-matched groups based on clinical assessment and CBCL/DP: typically developing controls without attention-deficit/hyperactivity disorder (ADHD) (n = 38), individuals with ADHD without the CBCL/DP (ADHD/DP−) (n = 38), and individuals with the CBCL/DP (CBCL/DP+) (n = 38). Groups were compared with EEG and measures of clinical phenomenology and cognition. **Results:** ADHD/DP− and CBCL/DP+ groups had increased inattention, but the CBCL/DP+ group had increased hyperactive/impulsive symptoms, disruptive behavior, mood, and anxiety comorbidities compared with the group with ADHD alone. Cognitive profiles suggested that ADHD/DP–participants had fast impulsive responses, whereas CBCL/DP+ participants were slow and inattentive. On EEG, CBCL/DP+ had a distinct profile of attenuated δ-band and elevated α-band spectral power in the central and parietal regions compared to ADHD/DP− and controls. The low-δ/high-α profile was correlated with measures of emotion and behavior problems and not with inattentive symptomatology or cognitive measures. There were no EEG differences between the ADHD/DP− and control groups. **Conclusions:** An EEG/cognitive profile suggests a distinct pattern of underlying neural dysfunction with the CBCL/DP that might ultimately serve as a biosignature. Further work is required to identify potential relationships with clinically defined psychiatric disorders, particularly those of dysregulated mood. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(11):1173–1182. **Key Words:** attention-deficit/hyperactivity disorder (ADHD), biological markers, brain imaging techniques, cognitive neuroscience, mood dysregulation

There is ongoing interest in the Child Behavior Checklist–Dysregulation Profile (CBCL/DP) as a measure of pediatric psychopathology.[1-3] The CBCL/DP is defined categorically in youth by clinical elevations on each of the standard CBCL Attention Problems, Aggression, and Anxious/Depressed subscales, or dimensionally as the sum of raw scores on the same.[4-6] The CBCL/DP has become widely regarded as a measure of emotional and behavioral dysregulation,[3, 6-10] with possible prognostic significance within heterogeneous groups of children with emotional and disruptive behavior disorders. The profile has been described as highly heritable,[11] and suggestive genetic associations support its potential validity as a distinct phenotype. Little research, however, has examined biological correlates of the CBCL/DP that might aid in its interpretation and further improve its predictive validity. This study attempts to identify associations of the profile with measures of cortical activation using electroencephalography (EEG), as well as assessments of behavior and cognition.

The CBCL/DP has demonstrated predictive value in phenomenological and longitudinal studies. Youth with the CBCL/DP show increased risk of anxiety,[12] mood disorders,[12,13]

disruptive behaviors,[13] substance abuse,[9,12] personality disorders,[12] suicidality,[8,9,12] psychiatric hospitalizations,[13] overall impairment,[8,9,14] and increased levels of psychosocial adversity.[14] In a family genetics study of attention-deficit/hyperactivity disorder (ADHD)–affected sibling pairs, individuals with the CBCL/DP had increased rates of lifetime anxiety and disruptive behavior disorders, as well as parental histories of substance abuse.[5] In preschoolers, the CBCL/DP was associated with significant behavioral and emotional dysregulation and maladaptive parenting.[10] The CBCL/DP predicts high novelty seeking, high harm avoidance, low reward dependence, and low persistence—traits associated with adult disorders of self-regulation such as those seen in cluster B personalities.[6] One longitudinal study using the CBCL/DP revealed that identified youth demonstrated increased rates of anxiety and disruptive behavior disorders as adults.[7]

Numerous studies suggest that the increased risks associated with the CBCL/DP are strongly mediated by genetic factors. Individuals with the CBCL/DP have increased likelihoods of having other siblings with similarly elevated scores.[13] The genetic architecture of the CBCL/DP has been described and reveals additive genetic effects, with heritability estimates ranging from 59% to 68%.[11] Candidate gene studies reveal possible associations with the dopamine transporter (*SLC6A3*) and brain-derived neurotrophic factor (*BDNF*).[15] Genome-wide linkage studies suggest potential loci (LOD scores > 2.5) on chromosomes 2q23,[5] and 1p21.1, 6p21.3, and 8q21.13.[16] One genome-wide association study found suggested evidence of a role for the CBCL/DP and genes implicated with hippocampal-dependent memory and learning.[15]

Despite some progress in describing the characteristics, family patterns, and heritability of the CBCL/DP, little is known about its possible neurobiological underpinnings. One small study using a tryptophan depletion paradigm suggested that individuals with higher scores on the CBCL/DP have alterations in serotonin functioning compared to those with lower scores, and that this is primarily mediated by the Aggression subscale.[17] A second preliminary report suggested that higher CBCL/DP scores are associated with increased basal levels of thyroid-stimulating hormone,[18] although another investigation found no relationship between the CBCL/DP and thyroid functioning.[17] A recent pilot investigation in 37 individuals using proton magnetic resonance spectroscopy revealed a significant correlation between glutamate concentrations in the anterior cingulate cortex (ACC) and CBCL/DP scores in the high CBCL/DP group, suggesting that impaired glutamatergic functioning in the ACC might underlie aspects of emotional dysregulation.[19]

EEG is a well-established noninvasive method of brain imaging that measures activity in functional neural systems and has been proposed as a potential biomarker for several disorders associated with impaired cognition.[20] EEG profiles are highly heritable and have proved successful as endophenotypes for genetic investigations of several psychiatric disorders.[21] A large body of literature on EEG differences between individuals with and without ADHD describes a predominant finding of increased frontocentral theta (θ)–band activity, which is thought to arise in part from the anterior cingulate.[22,23] A meta-analysis of 9 studies with a collective sample of 1,498 participants found an average excess of 32% θ-band power for children with ADHD relative to controls.[23] EEG spectral power differences in other frequency bands, such as elevated alpha (α)–band and attenuated beta (β)–band power, have been reported, although considerable variability in findings can be found throughout the literature. This variability has been attributed to sample characteristics such as age, sex, and ADHD subtype; however, emotional dysregulation has not been systematically studied.

EEG findings in the mood literature have focused on regional differences in α- band power. Previous studies have found higher α-band power synchrony, and connectivity among individuals with major depression[24-26] and emotion dysregulation,[27] when compared with controls. Additionally, studies have found increased central and parietal α-band power in depression[28,29] and melancholic temperament,[30] suggesting that α-band power might reflect affective dysregulation arising from the thalamocortical circuit.

In the current investigation, we were interested in determining whether the CBCL/DP might be associated with unique EEG, behavioral, and/or cognitive profiles that reveal additional information on brain functioning in identified individuals. Because the vast majority of children with the CBCL/DP have ADHD, it is of interest to determine whether distinct EEG profiles are associated with ADHD, prominent mood