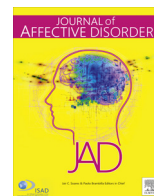




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Research paper

Empirically derived patterns of psychiatric symptoms in youth: A latent profile analysis



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ABSTRACT

Background: By conceptualizing domains of behavior transdiagnostically, the National Institute of Mental Health Research Domain Criteria (NIMH RDoC) initiative facilitates new ways of studying psychiatric symptoms. In this study, latent profile analysis (LPA) was used to empirically derive classes or patterns of psychiatric symptoms in youth that transect traditional nosologic boundaries.

Methods: Data were drawn from 509 children and adolescents (ages 7–18 years; mean age = 12.9 years; 54% male) who were evaluated in the NIMH Emotion and Development Branch and were heterogeneous with respect to presenting diagnoses and symptoms. Youth and/or their parents completed measures of several core symptom dimensions: irritability, anxiety, depression, and attention deficit hyperactivity disorder (ADHD). LPA was used to parse response patterns into distinct classes, based on the levels of, and interrelations among, scores on the different measures.

Results: Five classes emerged: low levels of symptomatology (52% of sample); anxiety and mild depressive symptoms (17%); parent-reported irritability and ADHD (16%); irritability and mixed comorbid symptoms (10%); and high levels of irritability, anxiety, depression, and ADHD (5%). Importantly, these latent classes cut across informants and the clinical conditions for which youth were initially evaluated. Further, the classes characterized by irritability exhibited the poorest overall functioning.

Limitations: These data were cross-sectional. Examination of external validators, including neurobiological correlates and symptom course, is warranted.

Conclusions: Results inform our understanding of the structure of psychiatric symptoms in youth and suggest new ways to operationalize psychopathology and examine it in relation to neurobiology.

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1. Introduction

Transdiagnostic constructs include neural, cognitive, and behavioral domains that transcend current clinical categories. The National Institute of Mental Health Research Domain Criteria (NIMH RDoC) initiative, recognizing limitations in current nosology, supports research on transdiagnostic constructs (Insel et al., 2010; Sanislow et al., 2010). Such work requires the creation of symptom-based dimensions from multiple DSM categories, which can be linked to measures of genetics and psychobiology (Garvey et al., 2016). Among youth, irritability and anxiety represent two dimensional, impairing, and correlated traits (e.g., Copeland et al.,

2015; Cornacchio et al., 2016; Savage et al., 2015; Stoddard et al., 2014), which may arise from shared biological vulnerabilities (i.e., multifinality, Cicchetti and Rogosch, 1996). Such interdependent relations among symptom dimensions have implications for the RDoC framework, but have yet to be empirically integrated (see Krueger and DeYoung, 2016). Limited research has examined how these symptom dimensions aggregate into classes, which may provide empirically derived alternatives to *a priori* DSM diagnoses. The current study uses latent profile analysis (LPA) to empirically identify multidimensional patterns or classes of psychiatric symptoms in youth from measures of these traits. The goal is to generate transdiagnostic symptom profiles, which might be examined in future research on neurobiology and genetics.

It is essential to study severe irritability and anxiety in youth in an integrative manner. Irritability refers to a propensity toward anger, including irritable mood, low frustration tolerance and temper outbursts (reviewed in Leibenluft, 2011). High levels of

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irritability in youth impair functioning (e.g., Copeland et al., 2013) and predict later risk for suicidality (Pickles et al., 2010; see meta-analysis of outcomes of pediatric irritability in Vidal-Ribas et al., 2016). Anxiety refers to the response to threats. Clinically significant anxiety is among the most prevalent pediatric clinical phenotypes (reviewed in Pine and Klein, 2015). Irritability aligns with the RDoC construct of frustrative nonreward (Dickstein, 2015), while anxiety aligns with the potential threat construct (Blackford and Pine, 2012). Although irritability and anxiety are often studied separately, they significantly co-vary in both community and clinical samples of youth (e.g., Cornacchio et al., 2016; Savage et al., 2015; Stoddard et al., 2014). Recent work suggests common biological substrates (Blair, 2010; Savage et al., 2015) and behavioral deficits (Hommer et al., 2014) across irritability and anxiety.

Previous studies have used factor analytic methods to examine the structure of psychopathology in youth (e.g., Burke et al., 2014; Krieger et al., 2013; Lahey et al., 2004, 2008; reviewed in Vidal-Ribas et al., 2016). These models provide insight into the average relations among symptoms or diagnoses within a population. In contrast, person-centered statistical techniques, such as latent class analysis (LCA), utilize individuals as the unit of analysis, with the purpose of identifying relatively homogeneous subgroups. These techniques have the key advantage of providing information about individuals (Goodman, 1974; Hagenaars and McCutcheon, 2002; Lazarsfeld and Henry, 1968). Most LCA studies use diagnostic or other categorical data (e.g., Olinio et al., 2012; Vaidyanathan et al., 2011). LPA, in the present study, differs from LCA in its use of *dimensional* class indicators (i.e., symptom dimensions), making it relevant to RDoC. Classes are derived empirically based on the levels of, and interrelations among, the dimensional indicators.

This study leveraged a large, carefully phenotyped pediatric sample to delineate multidimensional, transdiagnostic symptom profiles. Analyses targeted dimensional measures of irritability, anxiety, depressive, and attention deficit hyperactivity disorder (ADHD) symptoms, which have not been integrated previously using LPA. Symptoms of depression and ADHD were included because they often co-occur with irritability and anxiety (e.g., Brotman et al., 2006; Costello et al., 2003) and, similarly, may share biological mechanisms with irritability and/or anxiety (e.g., Eley and Stevenson, 1999; Savage et al., 2015; Stringaris et al., 2012b). Based on previous research (e.g., Brotman et al., 2006; Cornacchio et al., 2016; Costello et al., 2003; Savage et al., 2015; Stoddard et al., 2014), we hypothesized that the LPA would identify several different multidimensional symptom profiles, including classes of youth characterized by co-occurring irritability and anxiety, co-occurring irritability and ADHD, and co-occurring anxiety and depression, and that classes characterized by the greatest degree of symptom co-occurrence would exhibit the poorest functioning. Further, we hypothesized that the LPA would not conform to traditional diagnostic boundaries, such that the target conditions or diagnoses for which youth were initially evaluated would be distributed across the obtained classes.

2. Method

2.1. Participants

Five hundred and nine children and adolescents between the ages of 7 and 18 years were included in the LPA. Participants completed the symptom measures as part of research in the NIMH Emotion and Development Branch between 2012 and 2015. All procedures were approved by the NIMH Institutional Review Board. Parents gave written informed consent and youth gave written assent. Participants were recruited through advertisements.

Initial diagnostic interviews determined participants' eligibility for various research protocols, recruiting several clinical groups. The clinical groups included: severe mood dysregulation (Leibenluft, 2011; Leibenluft et al., 2003; on which DSM-5 disruptive mood dysregulation disorder subsequently was formulated)¹; anxiety disorder (comprising social anxiety disorder, generalized anxiety disorder, and/or separation anxiety disorder); ADHD; bipolar I or II disorder; first-degree relative of individual with bipolar I or II disorder and therefore at familial risk for the disorder; and healthy comparison participants with no current or lifetime diagnosis. First-degree relatives of individuals with bipolar disorder could not meet criteria for any bipolar spectrum disorder themselves; other diagnoses were allowed. Master's- and doctoral-level clinicians administered the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) separately to youth and parents to determine diagnoses based on *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR*; American Psychiatric Association, 2000) criteria. Diagnoses were based on best-estimate procedures generated in a consensus conference led by a senior psychiatrist. Exclusion criteria for all groups included: IQ below 70 or the presence of a severely-impairing pervasive developmental disorder, posttraumatic stress disorder, schizophrenia, substance use within the preceding three months, neurological disorder, or unstable medical illness.

2.2. Measures

2.2.1. Latent profile indicators

2.2.1.1. Affective Reactivity Index – Child- and Parent-Report (ARI; Stringaris et al., 2012a). The ARI assesses irritability in youth. Items probe both irritable mood (e.g., “easily annoyed by others”) and temper outbursts (e.g., “loses temper easily”) in the preceding six months. A total score (range=0–12) is determined separately for the Child- and Parent-Report forms by summing six items rated on 3-point Likert scales. The ARI is both valid and reliable (Stringaris et al., 2012a) and has been administered across a range of youth with mood and anxiety disorders (Stoddard et al., 2014). In the present sample, internal consistency was high among the items comprising the Child-Report total score (Cronbach's $\alpha=.85$) and Parent-Report total score ($\alpha=.93$). The Child- and Parent-Report total scores were correlated with one another ($r=.51, p<.001$).

2.2.1.2. Screen for Child Anxiety Related Disorders – Child- and Parent-Report (SCARED; Birmaher et al., 1999). The SCARED assesses symptoms of several different anxiety disorders in children and adolescents. Items refer to symptoms in the preceding three months and are rated on 3-point Likert scales. Ratings are summed to a total anxiety symptoms score (range=0–82) and subscale scores corresponding to different diagnoses. For the LPA, we utilized the separate Child- and Parent-Report total scores in order to be consistent with our inclusion of ARI child and parent total scores. The SCARED has been shown to be both valid and reliable (Birmaher et al., 1999). In the current sample, internal consistency was high among the items comprising the Child-Report total score ($\alpha=.95$) and Parent-Report total score ($\alpha=.95$). The Child- and Parent-Report total scores were correlated with one another ($r=.56, p<.001$).

2.2.1.3. Children's Depression Inventory (CDI; Kovacs, 1992). The CDI is a validated measure of self-reported depressive symptoms in youth. Each item presents three different statements referring to

¹ Research examining the prospective phenotype of severe mood dysregulation has indicated that 97% of these youth meet criteria for disruptive mood dysregulation disorder (DMDD) (Deveney et al., 2015; see also Stoddard et al., 2015; Tseng et al., 2016). Thus, we estimate that approximately 122 of the 126 SMD participants in the current analyses would meet DMDD criteria.

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