Age Effects in Manic Symptoms in Pediatric Bipolar Disorder

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ABSTRACT

ANDREW J. FREEMAN: Age Effects in Manic Symptoms in Pediatric Bipolar Disorder
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Pediatric bipolar disorder (PBD) remains a controversial diagnosis due in part to questions about the developmental appropriateness of manic symptoms. Three phenotypes have been proposed that differentially place importance on episodes, irritability, and elated mood/grandiosity. Participants were 1,395 outpatients (845 males) ages 5-17 years presenting from a mood disorders clinic or a community mental health clinic. Factor mixture modeling did not support developmentally distinct phenotypes. Confirmatory factor analysis with age as a covariate indicated small differences in ages. Regression analyses predicting comorbid diagnoses and CBCL subscales also displayed age differences. Limitations include that the sample is non-representative of outpatient clinics or epidemiological settings and symptom ratings were completed by the same caregiver. These findings affirm similar clinical presentations of manic symptoms across childhood and adolescence with different patterns of comorbidity.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

FIGURE

CHAPTER 1

INTRODUCTION

Pediatric bipolar disorder (PBD) is more common among children and adolescents than previously believed (Van Meter, Moreira, & Youngstrom, 2011). In the past twenty years, clinical PBD diagnoses have increased dramatically (Blader & Carlson, 2007; Harpaz-Rotem & Rosenheck, 2004; Moreno, et al., 2007) leading to controversy about both the existence (e.g., Hammen & Rudolph, 2003; Healy, 2006) and the phenomenology of the disorder (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). Similar to bipolar disorder in adults, PBD is characterized by periods of time during which individuals experience elevated mood, increased energy, irritability, and often grandiosity or decreased need for sleep (Cassidy, Yatham, Berk, & Grof, 2008; Kowatch, Youngstrom, Danielyan, & Findling, 2005; Youngstrom, Birmaher, & Findling, 2008). However, these are not the only symptoms of PBD. During hypomanic and manic episodes, individuals can also experience symptoms such as increased rate of speech and/or pressure to keep talking, flight of ideas or racing thoughts, increased distractibility, increase in goal-directed activity or psychomotor agitation, and excessive pleasure seeking (APA, 2000; Kowatch, Youngstrom, et al., 2005). Including all symptoms of PBD, there are 163 combinations of symptoms that could result in a diagnosis of bipolar I and over 5 billion combinations that could result in a diagnosis of any bipolar spectrum disorder (Lieberman, Peele, & Razavi, 2008). As a result, the potential for substantial heterogeneity exists in child, adolescent, and adult presentations,

which definitely contributes to the substantial inter-clinician diagnostic disagreement (Rettew, Lynch, Achenbach, Dumenci, & Ivanova, 2009).

The discrepancy in diagnosis is particularly significant for youths because retrospective studies of adults indicate that mood symptoms often begin during childhood and adolescence, and symptom onset prior to adulthood is associated with poor clinical outcomes such as increased risk of suicide (Angst, Stassen, Clayton, & Angst, 2002; Goldstein, et al., 2005), substance misuse (Wittchen, et al., 2007), and developing comorbid disorders (Leverich, et al., 2007). Even amongst children and adolescents with PBD, earlier age of onset is associated with negative clinical outcomes, such as increased risk for hospitalization, psychosis, suicide, and decreases in healthy school, peer, and family functioning (Birmaher & Axelson, 2006; Freeman, et al., 2009; Geller, Bolhofner, et al., 2000; Goldstein, et al., 2005). Evidence-based interventions in childhood and adolescent bipolar disorder are associated with reductions in symptoms (Haas, et al., 2009; Kowatch, et al., 2000; Tohen, et al., 2007; Wagner, et al., 2009), as well as improvements in quality of life (Rademacher, DelBello, Adler, Stanford, & Strakowski, 2007; Stewart, DelBello, Versavel, & Keller, 2009). Therefore, accurate, early assessment of potentially heterogeneous presentations followed by evidence-based treatment is one avenue for decreasing the burden of illness on children and adolescents.

The clinical variation in the presentation of mood symptoms and need for accurate assessment poses a dilemma for clinicians and researchers. The plethora of symptom combinations that could result in a diagnosis of PBD creates a situation in which heterogeneous presentation should be expected. Potential variation in symptom presentations across ages may contribute to the three overlapping, but discrepant models

for symptom presentation used today. First, the *narrow phenotype* requires the presence of elated mood and/or grandiosity in addition to other symptoms of mania, suggesting that irritability clusters with other "manic" symptoms independently of mania (Geller, Craney, et al., 2002; Leibenluft, et al., 2003). Geller and colleagues' initial investigation of the narrow phenotype focused on a sample that consisted primarily of adolescents or near-adolescent youth (mean age = 11 years). Second, the *broad phenotype* focuses on severe irritability with or without clearly defined episodes as a developmentally appropriate manifestation of bipolar disorder (Biederman, 1998; Wozniak, Biederman, Kiely, & Ablon, 1995). The earliest broad phenotype sample consisted of only children less than 12 years of age (mean age = 8 years) ascertained from a clinical infrastructure specializing in attention-deficit/hyperactivity disorder (ADHD). Third, the *intermediate phenotype* utilizes the DSM-IV-TR guidelines indicating that bipolar disorder in children and adolescents consists of distinct episodes during which the same symptoms occur as would define a mood episode in adults. The primary caveat of the intermediate phenotype is that some symptoms must be modified to be within the developmental repertoire of children and adolescents (Axelson, et al., 2006; Youngstrom, Birmaher, et al., 2008). For example, decreased need for sleep is a specific symptom of mania. Adults, and potentially older adolescents, displaying decreased need for sleep might work day and evening jobs without fatigue during manic episodes, whereas children and younger adolescents might stay up late re-arranging furniture or playing games and then wake up earlier than typical and attend school without fatigue during manic episodes (Geller, Zimerman, et al., 2002). The intermediate phenotype represents a middle ground between

the narrow and broad phenotypes as it allows for children and adolescents to display either presentation as long as the symptoms occur in the context of a mood episode.

Despite differences in the operational definitions of PBD, commonality between the three phenotypes does exist. A core set of children and adolescents meet criteria for PBD across all of these approaches. Children and adolescents diagnosed under the broad phenotype would also be diagnosed as PBD under the intermediate phenotype if they displayed episodic irritability plus four other mania symptoms. Additionally, youths could conceivably satisfy both broad phenotype and narrow phenotype criteria if they displayed episodic elated mood and/or grandiosity as well as irritable mood (although some proposals for the broad phenotype definition have made elated mood and/or grandiosity exclusionary criteria to avoid this, e.g., Leibenluft, et al., 2003). As displayed in Figure 1, approximately 20% of children and adolescents who meet criteria for the intermediate phenotype would *not* meet criteria for the narrow phenotype. The amount of non-overlap would most likely increase when comparing the broad and narrow phenotypes (Kowatch, Youngstrom, et al., 2005; Youngstrom, Birmaher, et al., 2008). Despite the differences in symptom clusters emphasized, the three phenotypes each assume that symptom clusters remain consistent over time. However, comparison of symptom presentation in different samples using different phenotypes suggest that younger presentations of PBD (age less than 12) include more irritability, mood dysregulation and comorbidity with ADHD and disruptive behavior disorders, whereas older presentations (age greater than 12 years) are more likely to display PBD more consistent with adult presentations including elated mood and grandiosity (Carlson, Bromet, & Sievers, 2000; Findling, et al., 2001; Geller, Craney, et al., 2002; Lewinsohn,

Klein, & Seeley, 1995; McClellan, McCurry, Snell, & DuBose, 1999; Strober, et al., 1995; Werry, McClellan, & Chard, 1991; Wozniak, et al., 1995). Consistent with the intermediate phenotype, current and proposed definitions of the PBD diagnosis advocate the use of a consistent set of symptoms across age and developmental periods (APA, 2000, 2010; W.H.O., 2004; Youngstrom, Birmaher, et al., 2008) and not the clinical use of the broad phenotype due to concerns that it is overly inclusive (Carlson & Meyer, 2000; Moreno, et al., 2007; Olfson, Crystal, Gerhard, Huang, & Carlson, 2009) and that children with chronic irritability might not develop (hypo)manic episodes (Brotman, et al., 2006; Stringaris, et al., 2010).

The primary purpose of the current study is to examine the possibility of symptom clusters differing across ages in children and adolescents in a clinically referred population. Examining differences in potential symptom clusters across childhood and adolescence could aid in resolving the appropriateness of each of the three models for clinical use as well as provide clinically significant information about typical symptom presentation across developmental ages in children and adolescents. If homotypic continuity, or similarly structured clusters, occurs across the age range, then the current use of the same set of symptoms as prescribed by the DSM-IV-TR would be appropriate, perhaps with minor modifications for expression or context to make them within the behavioral repertoire. If heterotypic continuity, or changes in the composition of symptom clusters, occurs across age, then stronger developmental considerations should be included in the definition of both pediatric mania and PBD.

Homotypic Models of Bipolar Disorder

Most construct validation studies in PBD have used the Robins and Guze (1970) criteria to delineate the disorder (e.g., Biederman, et al., 2003; Geller & Luby, 1997; Weckerly, 2002; Youngstrom, Birmaher, et al., 2008). The five criteria are: (a) clinical description of presenting symptoms; (b) laboratory studies differentiating the disorder from other disorders; (c) exclusion of other disorders; (d) follow-up studies to indicate homogenous groups displaying homotypic continuity of diagnosis and (e) family studies examining heritability of the disorder. With the Robins and Guze framework:

"The purpose of the follow-up study is to determine whether or not the original patients are suffering from some other defined disorder that could account for the original clinical picture. If they are suffering from another such illness, this finding suggests that the original patients did not comprise a homogenous group and that it is necessary to modify the diagnostic criteria… The same illness may have a variable prognosis, but until we know more about the fundamental nature of the common psychiatric illnesses marked differences in outcome should be regarded as a challenge to the validity of the original diagnosis" (p. 108).

In contrast to the homotypic continuity required by the Robins and Guze descriptive approach, developmental psychopathology attempts to define pathways of illness based on systematic dysfunction (Cicchetti, Cicchetti, & Cohen, 2006). *Equifinality* is the principle that dysfunction in multiple systems can result in the same outcome. From this approach, one might interpret differences in age of onset data – 60% during childhood and adolescence versus 40% in adulthood – as potentially representing evidence of multiple pathways, such as differences in genetic or environmental load,

leading to a similar phenotypic outcome (Chengappa, et al., 2003; Hirschfeld, Lewis, & Vornik, 2003; Leverich, et al., 2007; Perlis, et al., 2005). For example, pediatric bipolar disorder is associated with smaller amygdala volumes than age-matched healthy controls and adult bipolar disorder is not associated with amygdala differences (Usher, Leucht, Falkai, & Scherk, 2010). Therefore, the principle that multiple pathways result in the same disorder could be considered a reasonable assumption. Whereas equifinality might be interpreted as concerning the process of reaching a specific disorder or phenotypic copy, *multifinality* is the principle that an individual pathway could result in many different outcomes or disorders. In contrast to the multifinality principle, which suggests that systematic dysfunction could potentially lead to numerous alternate outcomes, the current principal assumption in bipolar disorders is that they are lifelong disorders that recur throughout the individual's lifetime (APA, 2000).

Due to public exposure to the concept in popular media as well as systematic research efforts, the rate of diagnosis for PBD has increased substantially – similar to increases observed in the past when depression (Kovacs, 1989) and panic disorder (Kearney & Silverman, 1992; Moreau & Weissman, 1992) were recognized as afflictions that children and adolescents could experience – and led to questions of whether PBD was similar to bipolar disorder in adults (Pavuluri, Birmaher, & Naylor, 2005). As a result, research focused on the homotypic continuity of diagnoses in PBD. Current efforts focus on displaying the continuity of PBD across childhood, adolescence, and early adulthood. Using the intermediate phenotype, diagnostic continuity was maintained for the majority of participants at both two and four year follow-ups (Birmaher, et al., 2009; Birmaher, et al., 2006). Prospective studies of relapse always involve some degree of

outcome censoring (i.e., the period of observation is not long enough for the outcome to occur, but it could still occur in some cases). In another set of studies using the narrow phenotype, Geller and colleagues (2002; 2008; 2004; 2000) have described the consistency of bipolar I diagnoses at six months and two, four, and eight year intervals. At the eight year interval, the majority of participants had entered into young adulthood and most continued to experience symptoms consistent with bipolar I disorder (Geller, et al., 2008). Combined with adult data suggesting long-term risk of relapse (Angst, 2000; Angst & Preisig, 1995), an adapted metaphor for bipolar disorder has been to compare the course of illness with cancer. An individual can be treated for cancer and cancer cells can be removed and/or controlled. Even after successful treatment, the risk of cancer cells re-growing or spreading remains; therefore, monitoring and caution are necessary. Likewise, mood episodes can be treated acutely and prophylactically prevented; however, the risk of relapse remains. For this reason both DSM-IV-TR and ICD-10 code people with a history of (hypo)mania as bipolar I, currently in remission, or bipolar II, currently in remission.

Using the Robins and Guze approach to developmental trajectories has caused most researchers to focus on the long-term homotypic continuity of bipolar disorder. These designs have not consistently accounted for the subset of individuals who stop presenting with manic, or any, mood symptoms during follow-up periods. Underlying the symptoms of mania and the diagnosis of bipolar disorder are interactions between biological and environmental pathways that may develop or activate during different developmental windows. Other disorders are marked by heterotypic continuity that reflects both environmental attributes as well as biological development of the human

brain. For example, the disruptive behavior disorders are sometimes considered hierarchical presentations of the most extreme youth at any given age because the specific cluster of symptoms changes with development (Farrington, 1997). For example, children who display high levels of aggression early tend to continue displaying high levels of aggression; however, as neural structures develop and interact with the environment with increasing age, a shift from mild direct physical hostility to more indirect delinquent behavior, as well as more severe physical aggression, is observed (Campbell, Pierce, Moore, & Marakovitz, 1996; Loeber, Farrington, Stouthamer-Loeber, Moffitt, & Caspi, 1998; Maughan, Pickles, Rowe, Costello, & Angold, 2000; Moffit, Caspi, Dickson, Silva, & Stanton, 1996; Tolan, Gorman-Smith, & Loeber, 2000). In PBD, a 10-year prospective follow-up of offspring of bipolar parents indicated a progression from increased energy, excessive talking, decreased sleep, aggression, and problems concentrating to affective symptoms including mood and energy changes, sleep difficulties, and excessive talking (Shaw, Egeland, Endicott, Allen, & Hostetter, 2005).Therefore, sufficient consideration and examination of symptoms of mania developing or changing over time is necessary.

In a heterotypic continuity approach to the categorical diagnosis of bipolar disorder, prospective studies suggest that anxiety and depression might be the early expressions of bipolar disorder. Adult data suggest that not only are depressive episodes often the first episode that comes to clinical attention, but also that on average approximately 1% of adults with depression experience hypomanic or manic episodes each year (Angst, 2000; Angst, Sellaro, Stassen, & Gamma, 2005; Coryell, Endicott, Maser, & Keller, 1995). Prospective studies of children and adolescents with depression

suggest that approximately one-third of individuals experiencing pre-pubescent major depression will convert to bipolar disorder during late adolescence and early adulthood (Geller, Fox, & Clark, 1994; Geller, Zimerman, Williams, Bolhofner, & Craney, 2001). Similarly, emerging findings in adults indicate that depression is often preceded by anxiety disorders both within episode and across age, suggesting that anxiety might be an even earlier precursor of bipolar disorder (Angst, et al., 2011; Brady & Kendall, 1992; Fiedorowicz, et al., 2011; Kessler, Zhao, Blazer, & Swartz, 1997; Lépine, Wittchen, & Essau, 1993; Lewinsohn, Zinbarg, Seeley, Lewinsohn, & Sack, 1997; Schneier, Johnson, Hornig, & Liebowitz, 1992). Thus, the heterotypic development of bipolar disorder could commence with anxiety followed by depression and eventually by hypomania or mania for a subgroup. In summary, diagnosis-level data strongly suggest the possibility of heterotypic development in PBD.

Heterotypic Development of Bipolar Disorder

Although most recent research in PBD has focused on homotypic continuity of diagnosis across the lifespan as a method of supporting the validity of a PBD diagnosis, there is also evidence of heterotypic development. For example, epidemiological research suggests developmentally-limited forms of bipolar disorder might exist. Approximately half of individuals who experience manic episodes during late adolescence do not experience manic episodes during their late twenties (Cicero, Epler, & Sher, 2009). In prospective studies of adults, only a small subgroup of individuals with sub threshold mania symptoms developed full threshold bipolar disorder; however, a larger subgroup developed depression (Regeer, et al., 2006; Shankman, et al., 2009). The primary limitations of these analyses were that they did not account for potential censoring of

outcome data due to limited follow-up periods and that depression was not considered part of the bipolar spectrum – despite the fact that a hypomanic episode combined with a major depression episode is the official definition of bipolar II disorder (APA, 2000). In contrast, three prospective studies of adults with bipolar disorder suggest that over the course of five to 40 years, between 16% - 24% fully remit and do not experience another mood episode (Angst, Gamma, et al., 2005; Angst & Preisig, 1995; Gitlin, Swendsen, Heller, & Hammen, 1995). Therefore, the potential for cessation of mood episodes exists. This raises the question of whether it should be possible to remove the diagnosis of bipolar disorder.

Prospective longitudinal studies of PBD suggest developmental changes across childhood and adolescence that might conceptually result in the loss of the capacity for recurrence of mood episodes that define bipolar disorder. On the one hand, approximately 70% of children and adolescents relapse repeatedly into manic episodes if bipolar I is defined using the narrow phenotype, but on the other hand, approximately 10% of children and adolescents did not relapse into manic or depressive episodes within 8 years of follow-up (Geller, Craney, et al., 2002; Geller, et al., 2008; Geller, et al., 2004). Expanding the definition to the intermediate phenotype, after four years approximately one-third of youth diagnosed with PBD remit with no relapses of mood episodes, one-third change diagnostic categories by having more severe or an increased number of manic symptoms, and one-third display no change in their diagnosis due to a single long-duration episode (20%) or multiple relapses of similar severity (10%) (Birmaher, et al., 2009). In prospective studies of ADHD, a putative prodrome for PBD, mania symptoms at baseline do not predict mania symptoms at up to a six year follow-up (Galanter, et al.,

2003; Hazell, Carr, Lewin, & Sly, 2003; Kim-Cohen, et al., 2003). The potential for outcome censoring exists in each of these analyses, as the primary period of manic episodes (early adulthood) has not been completed. Three alternate interpretations are also a possibility. First, individuals not developing into more severe forms of PBD are still developing and will eventually develop more severe presentations. Second, individuals who do not show mania later were initially misdiagnosed if called "bipolar." Third and most controversially, the results suggest that a developmentally limited form of manic symptoms for a subgroup of cases might exist (Findling, et al., 2010; Horwitz, et al., 2010).

Potential Model for Heterotypic Development of Pediatric Bipolar Disorder

At the diagnostic level, changes in diagnosis reflect changes in the underlying pattern of symptoms. For example, to change from bipolar II to bipolar I, an individual must increase the severity of symptoms and typically increases the duration of symptoms, as well as potentially add new manic symptoms. In contrast to examination of categorical change, little study of symptom change across time exists. Evidence suggests the factor structures of clinician-rated measures display invariance across childhood and adolescence (Frazier, et al., 2007; Youngstrom, Danielson, Findling, Gracious, & Calabrese, 2002). This prior work indicates that statistical invariance occurs when research clinicians make inquiries and judgments about symptoms occurring in the behavioral repertoire of children and adolescents (Kowatch, Fristad, et al., 2005; Quinn & Fristad, 2004). For example, adults displaying hypersexuality might engage in sex with multiple partners, whereas a child might make sexually suggestive statements and/or gestures (Geller, Zimerman, et al., 2002). In this developmentally modified framework,

symptoms of mania are invariant across ages; however, the recorded behaviors are qualitatively different across age groups.

Symptoms may represent a closer link to the underlying biology of mood dysregulation than does a diagnosis. A number of studies have attempted to define factors of mania for further consideration in relationship to biological traits as well as clinical interpretability. However, most studies are plagued by poor methodology, such as performing traditional factor analysis on item level data, assuming uncorrelated factors, and using poor selection criteria for the appropriate number of factors. These methods often reflect a discrepancy between the theory posited and the data analytic approach resulting in findings that are incongruous with theory due to the over-extraction of factors. Despite these substantial limitations, mania frequently is divided into at least two factors consisting of what has been labeled "sunny," euphoric symptoms, and "dark," irritable symptoms (Akiskal, Azorin, & Hantouche, 2003; Akiskal, et al., 2001; Angst, Adolfsson, et al., 2005; Hantouche, Angst, & Akiskal, 2003). Using an alternative labeling system that might be more reflective of the underlying neural systems, these factors might be relabeled "exuberance" (e.g., elated mood, more talkative, increased goal-activity, and psychomotor agitation/increased energy) and "under-controlled" (e.g., irritability, flight of ideas, racing thoughts, distractibility, and engagement in risky activities) (Stringaris, et al., 2010). Therefore, heterotypic change in the cluster of mania symptoms might be the result of the development of underlying neural systems that proximally regulate motivation or impulsivity pathways.

The behavioral activation system (BAS) and the behavioral inhibition system (BIS) are theorized to control the intensity with which individuals respond behaviorally

and affectively to different classes of stimuli (Gray, 1994). BAS and BIS are theorized to be the two primary motivational systems underlying bipolar disorder as well as depression and anxiety. The BAS is hypothesized to control positive-valenced and approach-oriented affect by governing goal-attainment behavior, reward seeking, and positive affect (Johnson, et al., 2000). Having high trait levels of BAS is a risk factor for developing hypomania and mania because a hyper-responsive BAS (also sometimes referred to as the Behavioral Facilitation System by DePue and colleagues) enhances positive affective responses and expression (Depue & Iacono, 1989; Depue, Krauss, & Spoont, 1987; Depue & Zald, 1993). For example, euthymic adults with bipolar disorder respond to positive events by displaying greater positive emotions than healthy controls (Gruber, Harvey, & Johnson, 2009; Gruber, Johnson, Oveis, & Keltner, 2008). BAS regulated behaviors in mania might be most closely measured by elated mood, increased goal-seeking behavior, increased grandiosity, decreased need for sleep, pressured speech, flight of ideas, and increased pleasure seeking (Depue, et al., 1987). In young adults with bipolar disorder, BAS measured three months prior to mood episodes prospectively predicted grandiosity, goal-directed activity, and psychomotor agitation after controlling for the overall severity of manic symptoms (Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007). In summation, BAS most likely predicts symptoms consistent with the "sunny" or "exuberance" factor of mania.

The BAS undergoes rapid development during adolescence in both healthy controls and youth with PBD (Urošević, Collins, Muetzel, Lim, & Luciana, 2012). The BAS consists of dopaminergic fibers that ascend from the substantia nigra and nucleus A10 in the ventral tegmental area to innervate parts of the frontal cortex, basal ganglia,

and limbic system (Gray, 1991). Studies of both adults and youth with bipolar disorder indicate structural and functional differences in the limbic system relative to healthy controls (Frazier, et al., 2005; Soares & Mann, 1997a, 1997b). This system is a dopamine pathway. The innervation and pruning of the dopaminergic system commences during childhood, but the primary developmental period is adolescence. During adolescence, levels of dopamine in the striatum significantly increase (Andersen, Dumont, & Teicher, 1997; Teicher, et al., 1993), dopamine receptor sensitivity increases (Seeman, et al., 1987), and volumetric decreases in regions of the basal ganglia occur (Giedd, et al., 1999; Giedd, et al., 1996). Behaviorally, dopamine release and sensitivity are greater during adolescence than childhood, which partially accounts for an increase in thrill seeking behavior (Lenroot & Giedd, 2006). Therefore, adolescents with PBD might experience symptoms more consistent with the narrow phenotype than children with PBD due to the greater sensitivity and activation of the BAS system.

In contrast, the BIS is hypothesized to control negative affect by responding to signals of punishment, non-reward, and fear stimuli and by inhibiting the BAS. Theoretically, the BIS might be responsible for switching to depressive episodes. For example, decreased BAS and increased BIS prospectively predict the onset of depression in young adults (Alloy, et al., 2008). Despite the common pairing of the BIS and BAS systems for bipolar disorder, the BIS does not predict mania (Alloy, et al., 2008; Johnson, Turner, & Iwata, 2003; Meyer, Johnson, & Carver, 1999). Instead, increase in BIS sensitivity with decrease in fun-seeking BAS drive predicts depressive episodes consistent with the tripartite model of depression. The BIS and BAS systems are bottom-up regulators of behavior because they reflect the neurobiological aspects of motivation.

In contrast to the bottom-up regulation of behaviors present in the BAS system, *effortful control* is a top-down regulator of behavior that also undergoes a developmental period during adolescence. Effortful control is the ability to inhibit socioaffective primary responses and perform a secondary response (Rothbart & Bates, 2006; Rothbart & Rueda, 2005). Effortful control represents the capacity to initiate, cease, and modulate one's initial behavioral motivation in accordance with external standards. Therefore in PBD, BAS dysregulation might increase the potential for positive affect while effortful control might inhibit the response. Prior work has not examined the role of effortful control in PBD. However, lower levels of effortful control are associated with higher levels of reactive irritability, motor agitation, and inattention (Calkins & Dedmon, 2000; Kochanska & Knaack, 2003; Kochanska, Murray, & Harlan, 2000). Additionally, lower levels of effortful control are associated with fewer internalizing problems, as anxiety and depression are often related to over-control (Eisenberg, et al., 2009; Stieben, et al., 2007). In case descriptions of six hospitalized preschool children with PBD, irritability, psychomotor agitation and inattention were present in most children, whereas grandiosity and pleasure seeking were not (Tumuluru, Weller, Fristad, & Weller, 2003). Therefore, PBD during childhood might be experienced as irritable and impulsive with low levels of depressive mood, consistent with a "low effortful control" hypothesis.

The effortful control system commences development during the 1st year of life, stabilizes during the early preschool years, and then develops again during late childhood (Kochanska, et al., 2000). Effortful control relies on activation of the anterior cingulate and lateral prefrontal areas, which mediate voluntary executive control mechanisms (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Thompson, Lewis, & Calkins, 2008).

The anterior cingulate activates in response to two neural systems being simultaneously activated, suggesting that its role is to detect competing neural system responses (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Rueda, et al., 2004). Relative to healthy controls, the anterior cingulate displays greater activation and impaired functioning to emotional tasks (Cerullo, Adler, Delbello, & Strakowski, 2009; Chang, et al., 2004; Strakowski, et al., 2005). The lateral prefrontal areas activate in attempts to reappraise the competing signals and plan a response (Ochsner, Bunge, Gross, & Gabrieli, 2002). Relative to healthy controls, the lateral prefrontral areas display greater activation and less development in bipolar disorder (Nugent, et al., 2006; Stanfield, et al., 2009). Both of these systems resume development of structural changes in pruning and myelination of neurons as well as the concentration of activation patterns during late childhood (starting at approximately 9 years) and complete development during early adulthood (Casey, Galvan, & Hare, 2005; Chugani, Phelps, & Mazziotta, 1987; Luna, Garver, Urban, Lazar, & Sweeney, 2004). If deficits in effortful control result in behaviors more consistent with the broad phenotype, then children with PBD might experience symptoms more consistent with the broad phenotype than adolescents with PBD.

As described above, heterotypic continuity appears at a diagnostic level in PBD. Extrapolations of typical development of the putative neural mechanisms strongly suggest that heterotypic continuity of symptom clusters could occur as displayed in Figure 2. The developmental trajectory of the BAS predicts that adolescents should experience symptoms of mania consistent with both the intermediate and narrow phenotypes – elated mood, grandiosity, goal-directed activity, motor agitation, and

pleasure seeking. Although some of these symptoms might also manifest at earlier ages, the developmental changes in BAS during adolescence should further increase these tendencies. Conversely, the developmental trajectory of the effortful control system predicts that children should experience symptoms of mania consistent with both the intermediate and broad phenotypes – irritability, motor agitation, impulsivity and inattention. Developmental increases in the capacity for effortful control are predicted to reduce the tendency to express these symptoms and behaviors. Motor agitation may represent an interesting example of equifinality, as it is associated with both high levels of BAS dysregulation and low levels of effortful control. However, the underlying mechanisms may be different, and it may be possible to differentiate them. BAS-related motor agitation should be episodic, as BAS is a response to external stimuli, whereas effortful control-related motor agitation should be more chronic, as effortful control is a general system that inhibits socio-affective responses. Intriguingly, this pair of predictions would be consistent with clinical observations that the bipolar presentation in younger cases may appear more chronically disinhibited, whereas in adolescents it might be more clearly episodic (Carlson & Meyer, 2000).

In addition to changes in symptom clusters predicted, the development of the BAS and effortful control neural systems should affect other behaviors displayed by youth. For example, the development of high levels of BAS is associated with substance use (Johnson, et al., 2003) and conduct problems (Fowles, 1980; Milich, Hartung, Martin, & Haigler, 1994; Quay, 1993) as well as PBD. Adolescents should display more problematic behaviors than children because their dopaminergic system is experiencing a period of risk in which it is hypersensitive to rewards relative to childhood as well as later

adulthood. In contrast, the attentional control system underlying effortful control develops during adolescence, along with associated reductions in impulsive and hyperactive behaviors (Shaw, et al., 2007; Shaw, et al., 2006). Therefore, comorbidity patterns associated with the clusters of BAS-related symptoms and low effortful control related symptoms should differ between children and adolescents. According to the BAS and effortful control hypotheses, adolescents should display more conduct disorder related problems, depressed mood, and episodic PBD. Based on the same model, children would be hypothesized to display more attention related problems, oppositional problems, and less episodic PBD.

Defining problematic clusters of symptoms and comorbidity is difficult because substantial disagreement exists amongst informants in general (Achenbach, McConaughy, & Howell, 1987) and in mania specifically (Youngstrom, Meyers, Youngstrom, Calabrese, & Findling, 2006b). Caregiver-reported symptoms of mania discriminate youth with PBD from youth without PBD better than self-report and teacher-report (Hazell, Lewin, & Carr, 1999; Youngstrom, Joseph, & Greene, 2008; Youngstrom, et al., 2005; Youngstrom, Meyers, Youngstrom, Calabrese, & Findling, 2006a). The disagreement between self-report and caregiver report is most likely due to lack of insight into the externalizing behaviors of mania (Dell'Osso, et al., 2002; Yen, Chen, Ko, Yen, & Huang, 2007) and the disagreement with teachers is most likely due to pre-existing assumptions about the cause of problematic behavior (Youngstrom, Joseph, et al., 2008). As a result, clinicians are often left with the difficult task of combining discrepant information to obtain an accurate picture of a youth's strengths and weaknesses. In studies of PBD, clinical researchers have used varying definitions of the behavior –

potentially biasing individual clinical ratings of mania symptoms (Galanter, et al., 2009; Geller, Zimerman, et al., 2002; Leibenluft, et al., 2003). Therefore, primary analyses in this study will be based on caregiver reported manic symptoms.

Goals of the Current Study

The goal of the current study is to identify potential clusters of mood symptoms and examine whether (a) their composition conforms to predictions based on broad or narrow phenotype definitions, and (b) determine whether the distribution across ages shows the hypothesized patterns of decreases in symptoms related to effortful control, or increases in BAS-related symptoms in adolescence.

Hypothesis 1. At least three clusters will emerge that reflect distinct profiles of manic symptoms consistent with the development of the BAS and effortful control neural systems. First, a cluster of all low scores will emerge that reflects individuals without mood dysregulation difficulties across the age spectrum. Second, a cluster consisting of high scores on irritability and inattention and low to moderate scores on grandiosity and elated mood will emerge (Broad). Third, a cluster consisting of high scores on grandiosity and elated mood and low to moderate scores on irritability, motor agitation, and inattention will emerge (Narrow).

Hypothesis 2. Age differences in class membership will occur. The average age of Broad class will be lower than the average age of the Narrow class.

Hypothesis 3. Clusters will display differential associations with measures of comorbidity consistent with the development of the BAS and effortful control neural systems. Hypothesis 3a: The primarily child-based cluster will display more difficulties with attention, oppositional problems, and aggression. Hypothesis 3b: the adolescent-

based cluster will display more difficulties with conduct-related problems and depressed mood.

CHAPTER 2

METHODS

Participants

Participants were 1,395 youth and caregiver pairs presenting at either an urban academic medical center (n = 793) or an urban community mental health center (n = 602) in the Midwest. Inclusion criteria for the current study at both sites were: (a) Youths between the ages of 5 years and 18 years, (b) both caregiver and youth provided written consent and assent, (c) both caregiver and youth presented for the assessment, and (d) both caregiver and youth were conversant in English. Table 1 displays the demographic characteristics of overall sample as well as demographic comparison of the two recruitment sites. Overall, participants presenting at the community mental health site were more likely to be African-American, slightly younger and have no mood disorder, whereas participants at the academic medical center were more likely to be Caucasian, slightly older and be diagnosed with bipolar I.

Recruitment. The academic medical center site had multiple pharmacotherapy trials open for bipolar spectrum disorders, unipolar depression, schizophrenia, attention-deficit/hyperactivity disorder, and post-traumatic stress disorder (as described in Findling et al., 2001). Youths were referred by local providers or responded to advertisements. Youths and caregivers willing to participate in treatment protocols were assessed if their initial symptoms reported during a phone screen appeared to match the enrollment

criteria for open trials. Additionally, the sample also included offspring of parents with bipolar disorder who were receiving treatment at an affiliated adult mood disorder clinic.

The community mental health site consisted of youths and caregivers presenting at a Midwestern urban clinic for treatment. Using a consecutive case series design at intake, all youth and caregiver pairs were asked to participate in an assessment research study. Data collection at the community mental health site was supported by R01 MH066647 (PI: E. Youngstrom). Data collection at the academic medical center was supported either by a Stanley Medical Research Institute grant (PI: R.L. Findling) or the NIH R01.

Measures

Schedule for Affective Disorders and Schizophrenia for Children (KSADS). The KSADS is a semi-structured interview that queries symptoms from common Axis I disorders from both the parent and child. Three versions of the KSADS were used in the current study. The KSADS-Epidemiologic version (KSADS-E, Orvaschel, 1995) was initially used at the academic medical center. The KSADS-E requires interviewers to complete every item with every participant (i.e., there were no "skip outs" from modules based on screening questions). The KSADS-Present & Lifetime version (KSADS-PL, Kaufman, et al., 1997) was used for most cases at the academic medical center. The KSADS-PL allows interviews to skip out of items depending on responses of the participant; however, all mood symptoms were administered to all participants regardless of eligibility to "skip out." At the community mental health center and for a subset of the academic medical center, the KSADS-PL-Plus version, which amalgamates the mood modules from the Washington University KSADS (Geller, Zimerman, Williams,

Bolhofner, Craney, et al., 2001) and the KSADS-PL (Kaufman, et al., 1997), was used. The Washington University KSADS includes additional symptoms and associated features of depression and mania beyond those included in the KSADS-PL version. At both sites, research assistants were highly trained: Symptom level ratings of new raters were compared with a reliable rater until passing five sessions rating along and then five leading the interview. A new rater passed a session if he/she achieved an overall $\kappa >= .85$ at the item level for the entire interview and a $\kappa = 1.0$ at the diagnostic level. A new cohort of raters was trained each year, and videotaped interviews were used to avoid drift across years. Research assistants were primarily predoctoral psychology interns or research staff with an MA or PhD in Psychology or an MSW. Research assistants conducted assessments at both sites.

Diagnoses. All cases at the community mental health center and a subset of cases at the academic medical center were reviewed using the Longitudinal Expert evaluation of All available Data (LEAD) procedure (Spitzer, 1983). Research assistants met with a licensed clinical psychologist to review the case. During the LEAD meeting, the research assistant presented the KSADS symptoms and diagnoses, family history, and information available from intake (e.g., intake diagnoses, chart review of diagnoses, prior treatment history, and school history). All members involved in the LEAD process were blind to all the questionnaires completed by caregivers.

At the academic site, diagnoses were determined after an additional assessment by licensed child psychiatrists. The child psychiatrist assessment included information about the participant's educational history and current living circumstances. Diagnoses were based on all available information including the KSADS interview, psychiatrists' clinical

interviewer, chart reviews, prior treatment history, and school history. All members of this diagnostic process were blind to all the questionnaires completed by caregivers.

Parent Report General Behavior Inventory (P-GBI). The parent report GBI modified the original self-report General Behavior Inventory (Depue, Krauss, Spoont, & Arbisi, 1989) so that all questions now query the caregiver about the mood and behavior of his/her offspring (Youngstrom, Findling, Danielson, & Calabrese, 2001). The P-GBI consists of 73 items measuring depressive, hypomanic, and mixed symptoms of mood disorder during the prior year. Participants answer "Never or Hardly Ever" to "Very Often or Almost Constantly" on a four point Likert-type scale about their offspring. For example, grandiosity is queried in the following manner: "Have there been times of a couple days or more when your child felt that he/she was a very important person or that his/her abilities or talents were better than most other people's?" Depressed mood is queried as follows: "Has your child become sad, depressed, or irritable for several days or more without really understanding why?" Mixed symptoms are queried in the following manner: "Has your child's mood or energy shifted rapidly back and forth from happy to sad or high to low?" The P-GBI consists of two scales—like the original GBI—Depression (Cronbach's $\alpha = .96$) and Hypomanic/Biphasic (Cronbach's $\alpha = .94$).

The Hypomanic/Biphasic scale measures symptoms associated with Mania in both classical and mixed forms. The 28 items will be divided into eight parcels consisting of three to four items each with fairly homogenous content (Youngstrom, et al., 2001). The eight parcels represent: 1) Enjoying pleasurable activities—items 2, 24, 35, 48 (Cronbach's $\alpha = .68$); 2) Rapid changes in mood—Items 19, 40, 53 (Cronbach's $\alpha = .81$); 3) Energy and activity—Items 4, 7, 15 (Cronbach's $\alpha = .75$); 4) Seeking pleasurable

activities—Items 22, 30, 31, 66 (Cronbach's α = .76); 5) Risk taking—Items 11, 17, 42, 51 (Cronbach's α = .69); 6) Irritability—Items 27, 44, 54 (Cronbach's α = .67); 7) Thought problems—Items 8, 57, 64 (Cronbach's α = .58); and 8) Grandiosity—Items 38, 43, 46, 61 (Cronbach's α = .61). Internal consistency coefficients for the individual parcels met recommendations for inclusion in research analyses.

Child Behavior Checklist (CBCL). The Achenbach Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) is among the most widely used measures of child and adolescent behavior problems in both research and clinical work. The CBCL consists of 118 items that query about behavior problems in youth ages 6 to 18. Caregivers of youth aged 5 years completed the CBCL 1.5-5.5 years (Achenbach & Rescorla, 2000). The CBCL consists of three general scales: Total problems, Externalizing problems, and Internalizing problems. Additionally, there are eight clinical sub-scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. Achenbach and Rescorla (2001) review extensive evidence for the reliability and validity of the CBCL scores in multiple samples.

The academic medical center site used the 1991 version of the CBCL for most participants (Achenbach, 1991) and the 2001 version for the remainder. In the revision, six rarely used or unscored items (e.g., allergy and asthma) were changed or replaced with new empirically supported items. The new items queried alcohol and tobacco use, delinquent behavior, failure to finish tasks, and anhedonia. In addition to the change in items, scale names were changed, and DSM-IV oriented scales were added.

CHAPTER 3

Analytic Plan

Descriptive Statistics

Data were aggregated in the Statistical Package for Social Sciences Version 19.0 or later. Descriptive statistics were obtained for the age of child, age of PBD onset, duration of PBD illness, gender, race/ethnicity, CBCL subtests, diagnoses, and each of the eight PGBI parcels.

Hypothesis 1: Number of Clusters

Mplus 7.0 fit factor mixture models (FMM) on the sum scores of the 8 PGBI parcels covarying for age, as depicted in Figure 3. FMM is a combination of the common factor model and the latent class model (Muthen & Shedden, 1999). FMM allows for situations in which the population varies along a continuous latent trait; however, subgroups can differ in respect to the symptom patterns of indicators for the latent trait. Therefore, FMM allows for the exploration of heterogeneous subgroups within a continuous latent trait.

Figure 3 displays the primary, ideal, fully measurement invariant model being examined. A series of 11 models were fit. First, a single class model was fit to provide a baseline measurement model to which future models can be compared; because only one class exists, the means cannot be structured for this baseline model. Second, a series of models increasing the number of classes to six was fit to help determine the appropriate number of classes. Third, restrictions on the means and loadings between classes were

increased such that non-invariant and fully invariant models were fit. The non-invariant allowed for restrictions only on intercept and factor loading parameters that did not display significant differences among classes. The fully invariant model imposed equality across factor loadings and intercepts.

The best model was selected using a combination of the minimization of Bayesian Information Criteria (BIC; Bozdogan, 1987) and Akaike Information Criteria (AIC; Akaike, 1974) and meaningful interpretability. Both the BIC and the AIC penalize the likelihood for a model by weighting sample size in combination with the number of parameters to create an index of fit because large numbers of parameters in large samples could result in "overfit" models. When AIC and BIC disagreed, the BIC was given initial preference because Monte Carlo simulations suggested that the BIC consistently selects the correct number of classes and AIC tended to select too many classes (Fraley & Raftery, 1998; Jedidi, Jagpal, & DeSarbo, 1997; Lubke & Neale, 2006; Nylund, Asparouhov, & Muthén, 2007). In addition to selecting classes based on empirical grounds, transition matrices were examined because the inclusion of additional classes could result in the splitting of a well-interpretable class into two poorly interpretable classes. Transition matrices display a comparison class membership of individuals from a lower number class (i.e., a two class model) to a higher numbered class (i.e., three class model).

Hypothesis 2. Associations Between Latent Class and Age of Youth

Provided that classes resembling what was predicted emerge, I would then conduct an independent samples *t*-test comparing the Broad and Narrow classes to determine whether the classes differed in terms of age. Additionally, the multinomial

regressions included in the factor mixture model would indicate whether age predicted change in class membership.

Hypothesis 3. Examination of Comorbidity Profiles

Two complementary methods were proposed to identify differences in comorbidity patterns. First, a series of chi-squares determined whether the different clusters display predicted differences in comorbidity. If chi-squared results were significant and displayed patterns in the predicted direction, this represents weak confirmation of the hypothesis. If chi-squared results were significant and display patterns in the opposite direction than predicted, then this would be taken as evidence of strong disconfirmation. Second, I proposed to conduct a series of regressions using cluster membership to predict subtest raw scores on the CBCL (raw scores used only the overlapping items amongst the three versions of the CBCL). Covariates included demographic variables (i.e., gender, ethnicity) as well as study site location so that differences in referral patterns between sites were not construed as meaningful effects. Raw scores were used because standardized scores potentially hide developmental differences given that three different age-normed sets of benchmarks were be used.

CHAPTER 4

RESULTS

Hypothesis 1: Number of Classes

Table 2 displays the results of the different factor mixture models (FMM) varying the number of classes and the type of measurement invariance. Lower values of AIC and BIC indicate better fit. The AIC, BIC, and sample size adjusted BIC (SSaBIC) all favor the two class model with intercepts varying. The two class solution represents a high (n = 678, 49%) and a low class (n = 717, 51%). Figure 4 displays the sample means for each of the parcels for the one through five class solutions. The class means for each of the eight parcels strongly suggest that the classes represent varying levels of a single, continuous dimension. Transition matrices displayed in Table 3 suggest that additional classes primarily represent the splitting of prior classes into finer gradients of severity. For example, the two class solution displays poor agreement with clinical diagnoses of PBD, $\kappa = 37$, $p < .01$. However, the two class solution displays near perfect agreement with a median split of the sum of the eight parcels (*Median* = 20), $\kappa = .89$, $p < .01$. Taken together, the data strongly suggest that the forced class solutions represent a continuous dimensional gradient and not distinct subclasses based on the mean scores of the parcels.

Hypothesis 2. Associations Between Latent Class and Age of Youth

Hypothesis 2 originally called for the mean comparison of youth ages by class membership to determine whether the "broad" class was younger than the "narrow" class.

The FMM solutions did not support the existence of "broad" and "narrow" classes. Instead, the solution supported gradations along a single continuous dimension. To test whether age is related to the severity in the latent trait of mania and whether it directly affects the individual items, the following analytic plan was utilized. First, a single dimension confirmatory factor analysis was fit. Second, age was added as a covariate to the mania latent trait. Third, age was individually tested as a predictor of each of the eight parcels. Fourth, a final solution integrating age as a covariate for the latent trait and the parcels was fit.

Table 2 also displays the fit indices for this process because a CFA is a single class, one factor solution. Examination of the fit indices indicates that a unidimensional factor with age predicting only the latent factor of mania fit poorly, RMSEA = .15, CFI = .88, SRMR = .13. In contrast when age predicted individual parcels, the overall fit of the model improved slightly, RMSEA = .15, CFI = .91, SRMR = .12. The AIC, BIC, SSaBIC, and the likelihood ratio test of nested models all support using the more complex model. Figure 5 displayed the final CFA model with standardized loadings. The results indicate that as a child's age increases his/her (a) enjoyment of pleasurable activities, (b) rapid changes in mood, (c) irritability, and (d) grandiosity all increase. In contrast as a child's age increases, his/her (a) energy and activity and (b) thought problems decrease. Taken together, these findings display very mild support for developmentally changing presentations of PBD. The findings are not in line with predictions based on the effortful control system. Additionally, the incremental changes are generally small. For example, the average intercept for a 16 year-old child for energy and activity is only .71 higher than a 6 year-old child. Taken together, these data suggest

that there are extremely mild developmental differences in the presentation of PBD between children and adolescents.

Hypothesis 3. Examination of Comorbidity Profiles

Hypothesis 3 originally called for identifying profiles of comorbidity by chi-squared analyses comparing class and diagnoses as well as predicting CBCL raw scores via multiple regression. However, the FMM modeling did not support the existence of the "broad" and "narrow" classes. Instead, the solution supported a gradient of severity along a single dimension. Therefore, a series of logistic regressions were conducted predicting common diagnostic categories and CBCL raw scores using a child's age as the primary predictor after controlling for current parent-reported depressive and manic/biphasic symptoms, bipolar diagnosis, gender, ethnicity, and site location. Diagnostic categories considered are attention-deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, and the presence of any anxiety disorder (e.g., generalized anxiety disorder, separation anxiety disorder, social phobia, post-traumatic stress disorder, etc.).

Diagnostic Categories. Table 4 displays the results of the logistic regressions predicting each of the diagnostic categories. Younger children were hypothesized to display more ADHD and ODD compared to older children. Overall, the logistic regression model predicted ADHD diagnosis (χ^2 (8) = 364.24, $p < .01$) and the step adding a youth's age was significant, χ^2 (1) = 32.24, $p < .01$. After controlling for gender, ethnicity, location, bipolar diagnosis, current depressive symptoms, and current manic/biphasic symptoms, younger children were more likely to be diagnosed with ADHD than older children, $b = -.12$, odds ratio = .89, $p < .01$. The age effect was not different for individuals with and without PBD, $b = .02$, odds ratio = 1.02, $p > .05$, step χ^2

(1) = .31, p = .58. Overall, the logistic regression model predicted ODD (χ^2 (8) = 97.01, p < .01) and the step adding a youth's age was significant, χ^2 (1) = 16.64, p < .01. Younger children were more likely to be diagnosed with ODD than older children after controlling for gender, ethnicity, location, bipolar diagnosis, current depressive symptoms, and current manic/biphasic symptoms, b = -.09, odds ratio = .92, p < .01. The age effect was not different for individuals with and without PBD, b = .03, odds ratio = 1.03, p > .05, step χ^2 (1) = .50, p = .48.

Older children were hypothesized to display more conduct disorder. Overall, the logistic regression model predicted having a conduct disorder diagnosis (χ^2 (8) = 88.83, p < .01) and the step adding a youth's age was significant, χ^2 (1) = 29.80, p < .01. After controlling for gender, ethnicity, location, bipolar diagnosis, current depressive symptoms, and current manic/biphasic symptoms, older children were more likely to be diagnosed with CD than younger children, b = .17, odds ratio = 1.18, p < .01. The age effect was not different for individuals with and without PBD, b = -.02, p > .05, step χ^2 (1) = .17, p = .68.

No hypothesis was made regarding anxiety disorders, and anxiety was included for exploratory reasons only. Overall, the logistic regression model predicted any anxiety diagnosis, χ^2 (8) = 86.03, p < .01. After controlling for gender, ethnicity, location, bipolar diagnosis, current depressive symptoms, and current manic/biphasic symptoms, a child's age was not associated with the presence of an anxiety disorder diagnosis, b = -.03, Odds Ratio = .98, p = .27, χ^2 (1) = 1.30, p = .26. Additionally, the age effect was not different for individuals with and without PBD, b = -.00, p > .05, step χ^2 (1) = .01, p = .93.

CBCL Symptom Profiles. Table 5 presents the regression results of the Effortful Control-related CBCL Scales –Attention Problems, Aggressive Behavior, Social Problems, ADHD, and ODD. Younger children were hypothesized to display more attention difficulties, oppositional symptoms, and aggressive symptoms. In support of the hypothesis regarding increased attention problems in younger children, they displayed more Attention Problems (β = -.13, Δr^2 = .01 , p < .05) and ADHD symptoms than older children, β = -.17, Δr^2 = .02 , p < .05. In support of the hypotheses about increased oppositional and aggressive symptoms in younger children, they displayed more Aggressive Behavior (β = -.14, Δr^2 = .02, p < .05), more ODD symptoms (β = -.11, Δr^2 = .01 , p < .05), and more Social Problems than older adolescents, β = -.26, Δr^2 = .05, p < .05. In general, there were no differences in age-related effects for children with and without PBD, all Δr^2 < .01, ps > .05. One exception to this is that on the Attention Problems scale, older children with PBD had more symptoms than older children without PBD, β = -.13, Δr^2 < .01, p < .05. However, this effect likely represents Type 1 error because it did not replicate on scales that reflect very similar and often overlapping set of items.

Table 6 presents the regression results of the BAS-related CBCL Scales – Anxious/Depressed, Withdrawn/Depressed, Rule-Breaking, Affective Disorders, and Conduct Problems. Older children were hypothesized to display more conduct problems and depressive symptoms than younger children. In terms of depressive symptoms, the findings are mixed. Older children displayed fewer Anxious/Depressed symptoms than younger children, β = -.14, Δr^2 = .02, p > .05. Older age was associated with more Withdrawn/Depressed symptoms, β = .07, Δr^2 < .01, p < .05. However, age was not

associated with DSM-IV Affective Problems, $\beta = .01$, $\Delta r^2 < .01$, $p > .05$. In terms of conduct-related problems, the findings were also mixed. Older children displayed more Rule-Breaking Behaviors than younger children ($\beta = .12$, $\Delta r^2 = .02$, $p < .05$) but were not specifically engaging in Conduct Problems differently than younger children, $\beta = .02$, $\Delta r^2 < .01$, $p > .05$.

CHAPTER 5

DISCUSSION

Our data indicate that symptoms of PBD do not neatly separate in distinct latent classes as predicted by the general discussion of phenotypes in PBD and distinct developmental periods of the neural system. Despite this lack of separation into classes, both differences in development of effortful control and the BAS were supported by the data. In terms of manic symptoms, adolescents displayed significantly higher levels of "narrow" phenotype symptoms consistent with predictions based on available data . In contrast, children displayed significantly higher levels of "broad" phenotype symptoms consistent with predictions in the literature (e.g., Geller, Craney, et al., 2002; McClellan, et al., 1999; Nusslock, et al., 2007; Tumuluru, et al., 2003; Wozniak, et al., 1995). However, both increases were small in magnitude, and the lack of separation into distinct classes implies that it would be difficult to identify reasonably distinct phenotypes for PBD for clinical purposes. Additionally, children's age was related to their general levels of comorbidity. At the diagnosis level, adolescents were more likely to be diagnosed with conduct disorder than children, and children were more likely to be diagnosed with ADHD and ODD than adolescents. In terms of symptom profiles, adolescents displayed more depressive symptoms than children, whereas children displayed more inattentive, aggressive, oppositional, and social difficulties than adolescents.

Children and adolescents were predicted to separate into distinct classes based on their symptom profile and age. These predictions were consistent with current discussions

of how to define and classify the role of controversial symptoms of PBD such as irritability, grandiosity, and elated mood (Biederman, 1998; Geller, Craney, et al., 2002) and developmental differences in the BAS and effortful control systems. Expert opinion about phenotypes, as well as the development of BAS in late childhood/early adolescence, suggests that adolescents will display a "narrow" phenotype of mania that includes elated mood and grandiosity. In contrast, expert opinion combined with a later, secondary development of the effortful control system suggests children will display a "broad" phenotype of mania that includes high levels of irritability and hyperactivity (Leibenluft, et al., 2003). In contrast to these predictions, the current data do not support developmentally distinct classes. Instead, the data strongly align with mania existing on a continuum. When latent categories are extracted, the categories represent differing levels of severity and not distinct profiles of symptoms. These findings are consistent with many experts who recommend the use of consistent symptom profiles across age and developmental periods (Axelson, et al., 2011; Ghaemi, et al., 2008; Youngstrom, Birmaher, et al., 2008), and they also corroborate the DSM-5 proposal to use consistent criteria for bipolar disorder, mania, and hypomania across the life span (Vieta & Phillips, 2007).

Second, children and adolescents were hypothesized to differentiate themselves based on their display of "narrow" and "broad" phenotype symptom profiles. Development of BAS in late childhood/early adolescence predicts an increase in elated mood, grandiosity, and pleasure seeking activities, whereas the secondary development of the effortful control system predicts decreases in irritability, impulsivity, and psychomotor agitation. Our data do not support distinct categories that would confirm these predictions. Therefore, a confirmatory factor analysis with

age predicting individual sets of manic symptoms was conducted. Overall, the data indicated that adolescents displayed more enjoyment of pleasurable activities, grandiosity, rapid changes in mood, and irritability than children. Children displayed more energy and hyperactivity and thought problems than adolescents. However, the mean differences between a 6 and a 16 year-old were very small suggesting that clinically meaningful differences in individuals would not be identifiable. Our findings are generally consistent with comparisons to other samples that vary as a function of age (e.g., Carlson, et al., 2000; Lewinsohn, et al., 1995; McClellan, et al., 1999) as well as the sole within-sample comparison of symptoms across differing ages (Demeter, et al., 2012) in that the average level of mania symptoms typically increases in adolescence. Additionally, our data are generally consistent with predictions from BAS development (Nusslock, et al., 2007) and not the effortful control literature (Kochanska & Knaack, 2003). Overall, the current data support mild, theoretical differences that are too small to be clinically meaningful.

Third, profiles of comorbidity between children and adolescents were hypothesized to differentiate themselves based primarily on distinct developmental periods of the BAS and effortful control system related to age. Children were hypothesized to display more ADHD and oppositional behaviors than adolescents because effortful control undergoes a period of secondary development in late childhood/early adolescence that typically results in a decrease in these behaviors (Kochanska & Knaack, 2003; Kochanska, et al., 2000). Adolescents were hypothesized to display more conduct problems and depressed mood because BAS undergoes a period of development in late childhood/early adolescence that typically results in an increase in these behaviors. Children were more likely to be diagnosed with ADHD and oppositional defiant

disorder as well as to display more inattentive, aggressive, oppositional, and social difficulties than adolescents, suggesting that the attenuation in these symptoms predicted by effortful control development is observable at a behavioral level even in youth with PBD. In contrast, the BAS-related predictions were not strongly supported. Adolescents displayed more withdrawn/depressed symptoms and rule-breaking behavior but not increases in diagnoses of conduct disorder. These findings are consistent with the comorbidity literature in PBD (Carlson & Meyer, 2006) as well as the broader literature concerning the development of the BAS and effortful control system (Eisenberg, et al., 2009; Kochanska, et al., 2000).

Implications

The current study finds mixed support for the original hypotheses. The current study does not support the categorization of symptom profiles. Clinicians should not seek and interpret distinct profiles of manic symptoms for children compared to adolescents. Instead, clinicians should remember to examine every symptom of mania because the symptoms co-occur together on a gradient of severity. In theoretical terms, symptom and diagnosis results display mixed support for the indirect behavioral effects associated with the development of the BAS and effortful control systems as incremental increases in developmental level, not as a distinct developmental periods. As children age into adolescence, comorbidity and mania symptoms display changes in degree, not quality.

Limitations

The current sample does not represent common clinical or epidemiological samples. The sample is a combination of a heavily enriched mood disorders research sample and a community mental health center sample. The combination of the two samples created a single, large sample that was

heavily enriched for youth with PBD. The large sample size, particularly the large number of youth with PBD, allowed for empirically derived latent categories to be extracted. In contrast to prior work that categorized age ranges and then predicted symptom profiles (Demeter, et al., 2012), the current sample empirically tested whether distinct profiles of mania symptoms occur based on the youths' age. Even so, replication of these findings in larger epidemiological datasets that sufficiently sample PBD is necessary to determine whether referral bias is at play in that youth with PBD seeking clinical services could differ from youth with PBD who do not seek services.

Another limitation is that most ratings were from a single rater, the primary caregiver. The findings could possibly be attributed to common variance within a single rater rather than the constructs of interest (Chang, van Witteloostuijn, & Eden, 2010; Podsakoff & Organ, 1986). In contrast to this concern, the current findings show similar results between clinician-rated outcomes and caregiver-rated outcomes. A strength of the current study is that it followed best practices in diagnostic procedures (i.e., Longitudinal Evaluation of All Available Data, Spitzer, 1983) as well as maximizing potential information based on informant (i.e., caregivers provide better accounting of mania symptoms than does self-report; Youngstrom, Freeman, & Jenkins, 2009; Youngstrom, et al., 2005). Replication of the current findings using clinician-reported symptoms is important because clinicians may sift signal from noise in a particular manner. The lack of categories found might reflect the noise of caregiver reports and not the true signal underlying PBD. However, clinicians might also be creating discrete categories in the diagnostic process artificially (Beauchaine & Waters, 2003).

Figure 1. Venn diagram of the overlap of the narrow, intermediate, and broad phenotypes of pediatric bipolar disorder.

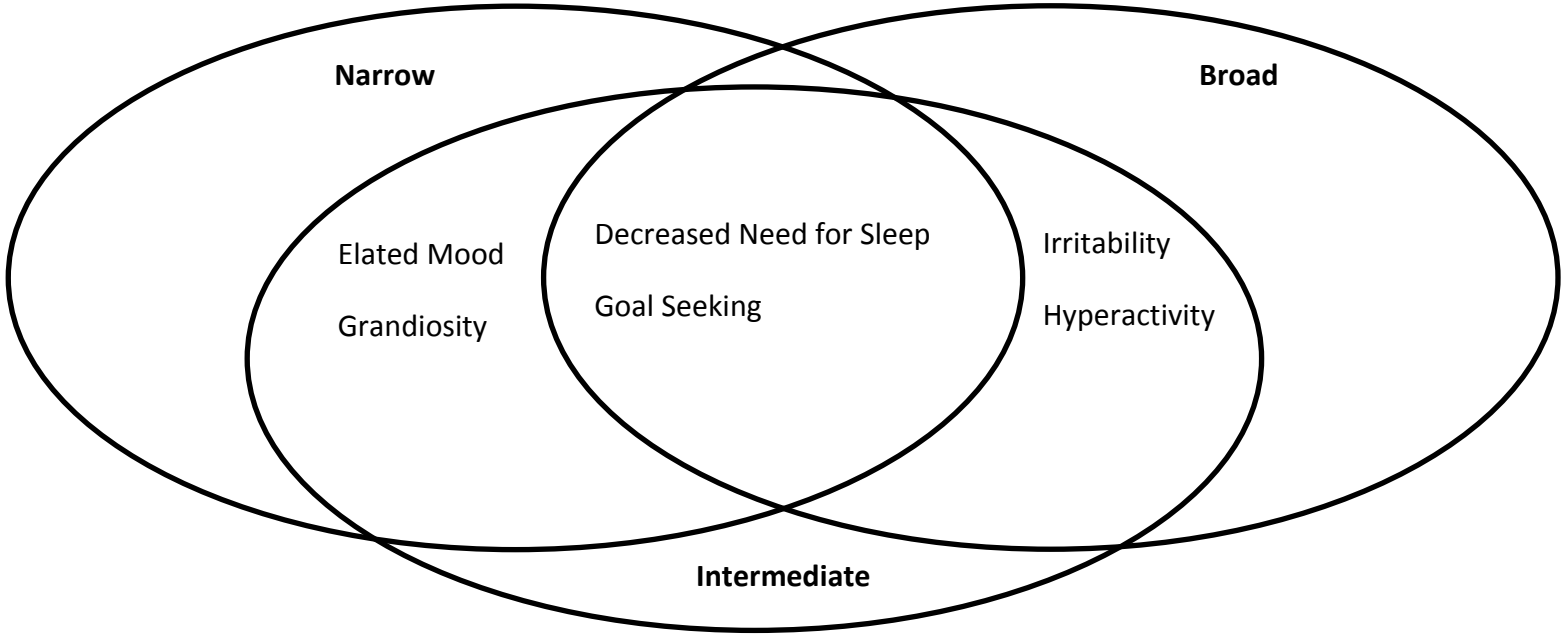


Figure 2. Hypothesized developmental trajectory of mania symptoms as predicted by development of the behavioral activation system and effortful control.

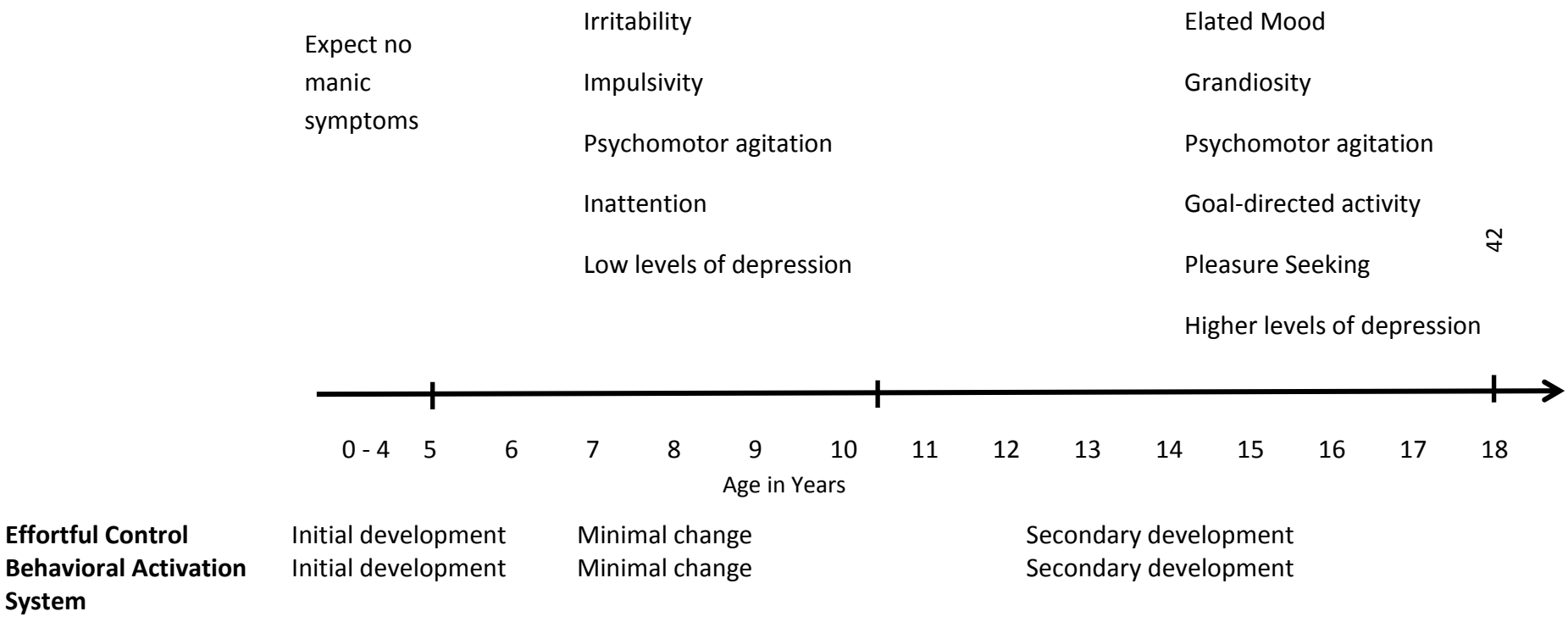
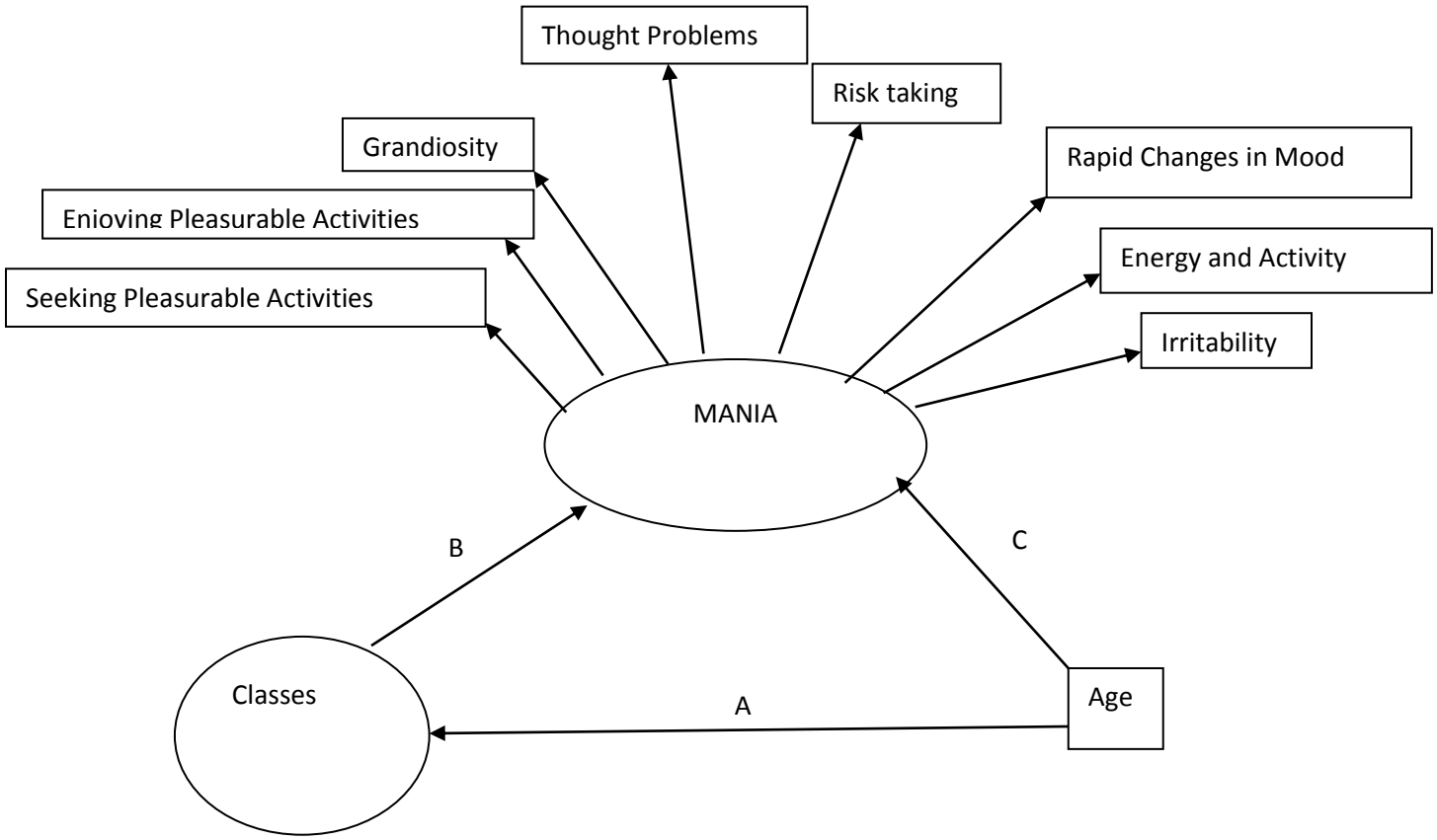
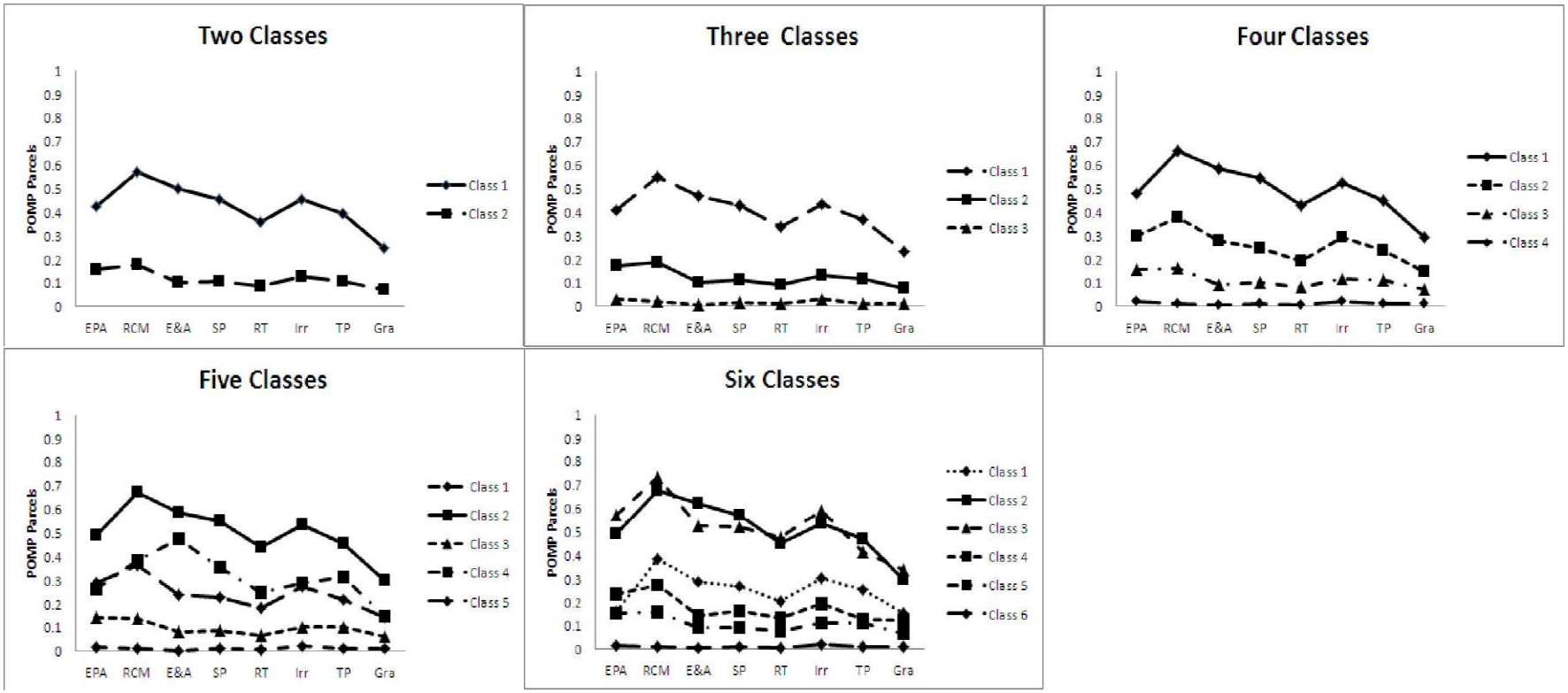


Figure 3. Ideal factor mixture model indicating that scores on the latent trait of mania depend on class membership covarying for age.



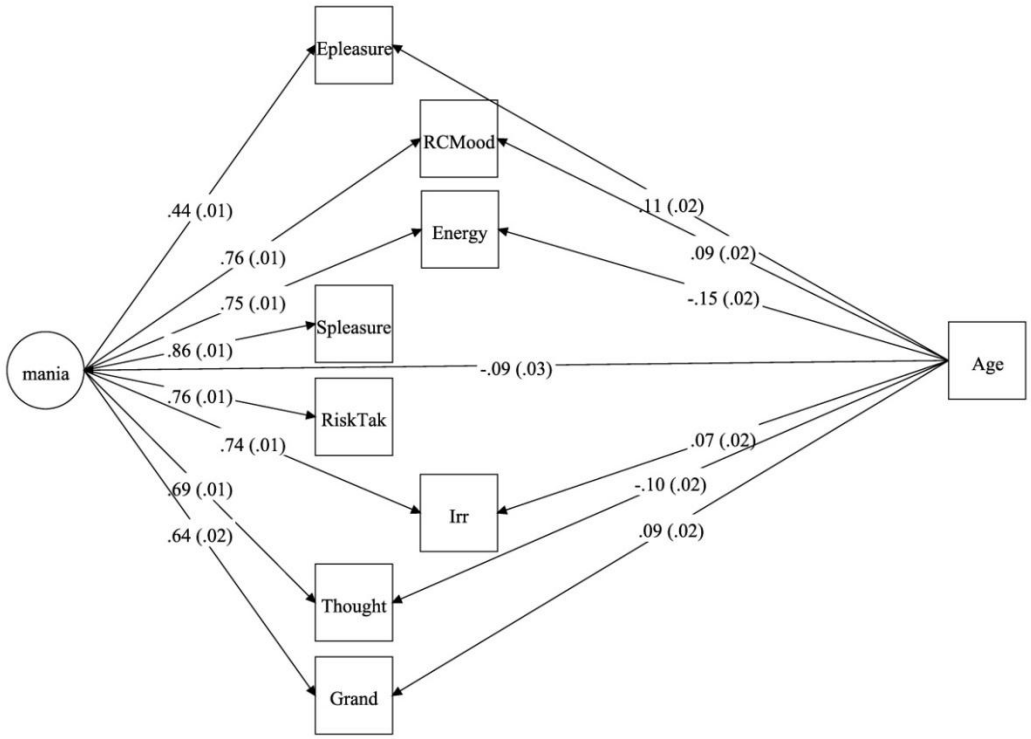
Note: A represents prediction of class membership based on age. B represents prediction of the score on mania based on class membership. C represents the effect of age predicting the score on mania.

Figure 4. Percent of Maximum Possible Sample Means for the Class Solutions.



Note: POMP = Percent of Maximum Possible. POMP scores place the parcel sum scores on a similar metric because parcels could have maximum scores of 9 or 12.

Figure 5. Confirmatory Factor Analysis with Age a Covariate of the Individual Symptom Parcels.



*_Note_: Epleasure: Enjoying pleasurable activities; RCMood: Rapid changes in mood; Energy: Increased energy and activity; Spleasure: Seeking pleasurable activities; RiskTak: Increased risk taking behavior; Irr: Irritability; Thought: Thought problems; Grand: Grandiosity

Table 1. Demographic characteristics of the Academic site, Community site, and Overall.

	Academic (*n*=793)	**Community (*n*=602)**	**Overall (*n*=1395)**
Gender			
Male *n* (%)	480 (61)	365 (61)	845 (61)
Female *n* (%)	313 (40)	237 (39)	550 (39)
Ethnicity*			
Caucasian *n* (%)	615 (78)	39 (6)	638 (46)
African American *n* (%)	106 (13)	532 (88)	654 (47)
Age in years* *M* (*SD*)	11.4 (3.3)	10.6 (3.4)	11.1 (3.4)
Number of Diagnoses* *M* (*SD*)	2.1 (1.3)	2.6 (1.3)	2.4 (1.3)
Primary Diagnosis*			
Bipolar I *n* (%)	173 (22)	16 (3)	189 (14)
Other Bipolar Spectrum *n* (%)	162 (20)	58 (10)	220 (16)
Unipolar Depression *n* (%)	187 (24)	171 (29)	358 (26)
Disruptive Behavior Disorder *n* (%)	184 (23)	298 (49)	482 (34)
All other diagnoses *n* (%)	87 (11)	59 (10)	146 (10)

*$p < .05$.

Table 2. Fit Indices for the Factor Mixture Model of Mania Parcels Covarying for Age.

Classes	Varying	Parameters	-2Log Likelihood	AIC	BIC	ssaBIC	Entropy
1							
	None	24	-22904.32	45856.64	45982.63	45906.39	
	Intercepts	29	-22458.88	45685.56	45837.81	45745.69	
2							
	None	29	-22628.31	45314.62	45466.87	45374.75	.54
	Intercepts	33	-22558.13	45182.27	45355.51	45250.68	.74
	Intercepts & Loadings	39	-22494.81	45073.62	45294.12	45160.70	.78
3							
	None	32	-22598.01	45260.02	45428.01	45326.36	.68
	Intercepts	36	-22644.42	45352.85	45520.84	45419.19	.89
	Intercepts & Loadings	38	-22658.13	45471.41	45601.42	45523.99	.90
4							
	None	36	-22562.41	45196.82	45385.82	45271.46	.65
	Intercepts	40	-22635.49	45344.99	45539.24	45421.70	.89
	Intercepts & Loadings	48	-22700.11	45498.14	45701.37	45615.78	.91
5							
	None	40	-22556.80	45193.60	45403.60	45271.46	.65
	Intercepts	43	-22632.09	45344.17	45554.17	45427.10	.85
	Intercepts & Loadings	50	-22702.01	45501.64	45762.84	45647.86	.87
6							
	None	44	-22551.64	45191.28	45422.27	45282.50	.73
	Intercepts	47	-22630.22	45346.43	45572.18	45435.58	.92
	Intercepts & Loadings	56	-22627.49	45493.23	45804.91	45764.42	.94

Table 3. Class Membership Transitions from Prior Classes.

Classes	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
One	**1395**	-	-	-	-	-
Two	**717**	**678**	-	-	-	-
From 1	717	0	0	-	-	-
From 2	88	463	127	-	-	-
Three	**805**	**463**	**127**	-	-	-
From 1	481	320	4	0	-	-
From 2	0	54	404	5	-	-
From 3	0	0	19	108	-	-
Four	**481**	**374**	**427**	**113**	-	-
From 1	0	449	0	32	0	-
From 2	0	7	0	22	345	-
From 3	0	0	340	3	84	-
From 4	105	0	8	0	0	-
Five	**105**	**456**	**348**	**57**	**429**	**-**
From 1	0	0	0	2	0	103
From 2	60	354	42	0	0	0
From 3	0	0	0	37	306	5
From 4	30	24	0	0	3	0
From 5	310	0	8	58	53	0
Six	**400**	**378**	**50**	**97**	**362**	**108**

Note: Bold numbers indicate the final class solution *ns*. An example of how to read the table for the transition from the two class to the three class solution is as follows. In the three class solution, 805 individuals are in class 3, and 717 individuals come from class 1 and 88 individuals come from class 2 of the two class solution. All 463 in class 2 and 127 in class 3 of the three class solution come from splitting class 2 of the two class solution.

Table 4. Logistic Regressions Predicting Diagnostic Comorbidity from Youth Age in Years.

	ADHD		*ODD*		*CD*		*Anxiety*	
	b	Odds Ratio (95% C.I.)	b	Odds Ratio (95% C.I.)	b	Odds Ratio (95% C.I.)	b	Odds Ratio (95% C.I.)
Intercept	1.21*	.41	-.34	.71	-4.00*	.02	-1.16*	1.47 (1.10 – 1.95)
Gender (1=female)	-1.11*	1.07 (.26 - .43)	-.29*	.75 (.59 - .96)	-.43*	.65 (.44 - .96)	.38*	.88 (.58 – 1.35)
Ethnicity (1 = Non-White)	.07	.72 (.75 – 1.52)	.04	.96 (.69 – 1.33)	.59*	1.80 (1.10 – 2.95)	-.12	.31 (.20 - .48)
Location (1 = Academic)	-.33	.98 (.50 – 1.03)	-.30	.74 (.53 – 1.05)	-.37	.69 (.42 – 1.14)	-1.17*	1.47 (.76 – 2.86)
PBD (1 = Yes)	-.02	.97 (.52 – 1.87)	-.17	.85 (.50 – 1.43)	.41	1.51 (.65 – 3.52)	.39	1.03 (1.02 – 1.04)
Depressive Symptoms	-.04*	.97 (.96 - .97)	-.01*	.99 (.98 – 1.00)	-.03*	.98 (.96 - .99)	.03*	.97 (.96 - .99)
Manic/Biphasic Symptoms	.08*	1.08 (1.06 – 1.09)	.03*	1.04 (1.02 – 1.05)	.06*	1.06 (1.04 – 1.08)	-.03*	.98 (.93 – 1.03)
Age in Years	-.12*	.89 (.85 - .93)	-.09*	.92 (.88 - .96)	.17*	1.18 (1.10 – 1.27)	-.03	1.00 (.91 – 1.09)
PBD by Age Interaction	.02	1.02 (.94 – 1.11)	.03	1.03 (.95 – 1.11)	-.02	.98 (.88 – 1.09)	-.00	1.00 (.91 – 1.09)
Nagelkerke R^2	.31*		.09*		.13*		.10*	

*$p < .05$.

Note: Nagelkerke R^2 is for the overall model.

Table 5. Hierarchical Regressions Predicting Effortful Control Related CBCL Subscales.

	Syndrome Scales						DSM-IV Scales			
	Attention		Aggressive		Social		ADHD		ODD	
	b (95% C.I.)	β	b (95% C.I.)	β	B (95% C.I.)	β	b (95% C.I.)	β	b (95% C.I.)	β
Intercept	6.78 (5.97 – 7.58)		13.59 (11.92 – 15.27)		6.61 (5.70 – 7.52)		5.19 (4.64 – 5.74)		5.66 (5.09 – 6.23)	
Gender (1 = Female)	-1.46 (-1.88 - -1.04)	-.18*	-.91 (-1.78 - -.04)	-.05*	.07 (-.41 - .54)	.01	-.63 (-.92 - -.35)	-.10	-.42 (-.42 -.72)	-.07*
Ethnicity (1 = Non-White)	.75 (.17 – 1.33)	.09*	-.91 (-1.78 - -.04)	-.05*	.22 (-.43 - .88)	.03	.52 (.12 - .91)	.09*	.40 (-.01 - .82)	.07
Location (1 = Academic)	-.26 (-.87 - .34)	-.03	1.49 (.28 – 2.71)	.08*	-.81 (-1.49 - .13)	-.09*	-.48 (-.89 - .07)	-.08	-.53 (-.96 - -.10)	-.09*
PBD (1 = Yes)	-.92 (-1.94 - .10)	-.10	3.16 (1.04 – 5.23)	.16*	-.27 (-1.42 - .88)	-.03*	-.09 (-.79 - .60)	-.01	.65 (-.08 – 1.38)	.10
Depressive Symptoms	.01 (-.00 - .02)	.05	.02 (-.00 - .05)	.06	.05 (.04 - .07)	.28*	-.02 (-.03 - -.02)	-.19*	-.00 (-.01 - .01)	-.02
Manic/Biphasic Symptoms	.10 (.08 - .12)	.38*	.25 (.20 - .29)	.43*	.05 (.03 - .07)	.17*	.12 (.10 - .13)	.61*	.07 (.06 - .09)	.39*
Age	-.16 (-.24 - -.09)	-.13*	-.38 (-.53 - -.22)	-.14*	-.36 (-.45 - -.28)	-.26*	-.17 (-.22 - -.12)	-.18*	-.09 (-.15 - -.04)	-.11*
PBD by Age Interaction	.16 (.02 - .30)	.13*	-.01 (-.30 - .27)	-.01	.07 (-.09 - .22)	.05	.07 (-.03 - .16)	.07	.04 (-.05 - .14)	.05
R^2	.23*	.	.34*		.22*		.35*		.23*	

*$p < .05$.

Note: R^2 is for the overall model.

Table 6. Hierarchical Regression Predicting Behavioral Activation Related CBCL Subscales.

	Syndrome Scales						DSM-IV Scales			
	Anxious/Depressed		Withdrawn/Depressed		Rule-Breaking		Affective		CD	
	b (95% C.I.)	β	b (95% C.I.)	β	b (95% C.I.)	β	b (95% C.I.)	β	b (95% C.I.)	β
Intercept	5.27 (4.21 – 6.33)		2.53 (1.91 – 3.16)		2.28 (1.20 – 3.37)		2.61 (1.73 – 350)		4.95 (3.51 – 6.39)	
Gender (1 = Female)	.32 (-.23 - .87)	.03	.06 (-.26 - .39)	.01	-.85 (-1.41 - -.28)	-.08*	.22 (-.24 - .68)	.02	-1.53 (-2.28 - -.77)	-.11*
Ethnicity (1 = Non-White)	-.36 (-1.13 - .41)	-.03	.06 (-.39 - .51)	.01	1.96 (1.17 – 2.74)	.19*	-.25 (-.90 - .39)	-.03*	2.48 (1.44 – 3.52)	.17*
Location (1 = Academic)	.30 (-.49 – 1.09)	.03	-.64 (-1.11 - -.18)	-.09*	-.08 (-.90 - .73)	-.01	.72 (.05 – 1.38)	.07*	-.84 (-1.92 - .25)	-.06
PBD (1 = Yes)	.71 (-.64 – 2.05)	.06	.61 (-.18 – 1.40)	.08	-.26 (-1.63 – 1.12)	-.02	.66 (-.46 – 1.78)	.06	1.29 (-.55 – 3.12)	.08
Depressive Symptoms	.13 (.12 - .15)	.58*	.11 (.10 - .12)	.76*	-.01 (-.02 - .01)	-.03	.13 (.11 - .14)	.64*	-.01 (-.03 -.01)	-.04
Manic/Biphasic Symptoms	-.01 (-.04 - .01)	-.04	-.07 (-.08 - -.05)	-.30*	.12 (.10 - .15)	.37*	-.03 (-.05 - -.01)	-.09*	.18 (.14 - .22)	.40*
Age	-.24 (-.34 - -.14)	-.14*	.08 (.02 - .14)	.07*	.20 (.09 - .30)	.12*	.01 (-.08 - .09)	.01	.05 (-.09 - .19)	.02
PBD by Age Interaction	-.02 (-.20 - .16)	-.01	-.07 (-.18 - .03)	-.07	.12 (-.06 - .31)	.08	-.01 (-.16 - .14)	-.01	.09 (-.16 - .33)	.04
R^2	.32*		.35*		.18*		.39*		.23*	

*$p < .05$.

Note: R^2 is for the overall model.

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