COMORBIDITY & CHILDHOOD PSYCHOPATHOLOGY: RELATIONS TO PROFILES OF BEHAVIOR AND NEUROANATOMY

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ABSTRACT

Childhood psychopathology refers to a heterogeneous set of psychological conditions that negatively influence functioning. To improve treatment, effort has been directed at defining, and categorizing disorders. The Diagnostic and Statistical Manual, the primary source for diagnostic information in the US, updates diagnostic criteria to parallel research and clinical advances. Nevertheless, much symptom overlap remains across conditions, complicating diagnosis and slowing research progress. Latent class analysis (LCA), a person-centered analytic approach, was used to explore new diagnostic groupings based on primary and comorbid diagnostic data from children with a diagnosis of Autistic Disorder or Asperger's Syndrome (ASD) (n = 76) or Bipolar Disorder (BPD) (n = 36), compared to 27 controls. LCA was expected to identify a subset of children with high comorbidity who would demonstrate distinct neuroanatomical and behavioral profiles. Comparison of the temporal cortex, amygdala, or hippocampus volumes between the diagnostic groups, and between the derived clinical latent classes, revealed no significant differences. The diagnostic groups were different on several problem behavior subscales, as were the latent classes. All clinical groups had more behavioral problems compared to controls. Although results did not support the use of comorbid information to improve diagnostic profiles, large within-group variances in the primary diagnostic groups supported the need to improve differential diagnoses. The DSM-IV categorical classification system is limited in its ability to characterize 'comorbid' symptomology. In the DSM-V, inclusion of a dimensional component and 'cross cutting' symptoms would provide clinicians with a useful way to differentiate disorders and evaluate symptom severity.

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CHAPTER I

Introduction

Childhood psychopathology is a broad term that refers to a heterogeneous set of psychological conditions that can have a significant negative impact on a child's development, as well as their functioning at home, in school, and in society. In order to improve access to both psychological and pharmacological treatment, researchers and clinicians have placed significant effort into identifying, defining, and categorizing childhood disorders. The Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2000) is the primary source for psychiatric diagnostic information in the United States, but this manual is not static; as research and clinical advances in neurobiology and psychology transpire, the DSM evolves and its diagnostic criteria change. As a result of these changes, diagnostic criteria are refined, disorders are better understood, and professionals are more easily able to distinguish primary diagnosis from co-occurring symptoms and associated features. More accurate diagnosis means better opportunities for early identification and optimal treatment. In addition, it means that co-occurring symptoms that may not be related to the primary diagnosis may be more accurately parsed out and identified as diagnostic criteria of other comorbid conditions.

This dissertation explores a person-centered analytic approach to classify children with psychopathology using primary and comorbid diagnostic information in an effort to empirically identify groups that are more homogeneous within groups but maximally

different from others. In addition, this dissertation examines distinctive patterns of neuroanatomical and behavioral profiles that are associated with the newly identified groups.

Primary Diagnosis

In recent years, Bipolar Disorder (BPD) and Autism Spectrum Disorders (ASD) have received a great deal of both professional and public attention. Considerable effort has been placed on identifying accurate diagnostic criteria and understanding the etiological processes related to these disorders. Nonetheless, accurately distinguishing between the primary diagnostic symptoms of a disorder and the associated features that often co-occur remains difficult.

Bipolar Disorder

Traditionally, BPD is categorized into BPD-I and BPD-II. In adults, BPD-I is characterized by the occurrence of one or more manic or mixed episodes, and often includes one or more major depressive episodes (American Psychiatric Association, 2000). BPD-II on the other hand, is characterized by one or more major depressive episodes, as well as at least one hypomanic episode (American Psychiatric Association, 2000). In the general population, the lifetime prevalence rates of BPD-I and BPD-II are estimated at 0.4-1.6% and 0.5%, respectively (American Psychiatric Association, 2000). In addition to the main diagnostic criteria, there are a number of associated but non-diagnostic features, such as school truancy, school failure, occupational failure, divorce, or episodic antisocial behavior (American Psychiatric Association, 2000). Moreover, BPD is associated with other disorders, including attention deficit hyperactivity disorder (ADHD), social phobia, panic disorder, and eating disorders (American Psychiatric

Association, 2000), possibly suggesting substantial overlap in diagnostic criteria or similar aspects of presentation across these conditions.

Traditionally, BPD has been thought of as a disorder of adolescence and adulthood. In fact, prior to 1990, many professionals believed that BPD was exclusively a disorder of adulthood and that it could not be diagnosed in children (Carlson & Strober, 1978). Controversy persists over the existence of pediatric BPD, but increasingly professionals are focusing their efforts on the intricacies and differences of its presentation in youth compared to adults (Dickstein & Leibenluft, 2006). One of the main controversies surrounding a diagnosis of pediatric BPD stems from its similarity to frequently occurring comorbid disorders. Specifically, BPD commonly co-occurs with disorders such as ADHD (Wozniak, Biederman, Kiely, Ablon, & et al., 1995), anxiety disorders (Dickstein, et al., 2005), and substance use disorders (Wilens, 1999). Because of the extensive overlap in symptomology, clinicians often find it difficult to attribute a given symptom specifically to BPD.

The DSM-IV-TR includes irritable and elevated/expansive mood as one criterion of BPD (American Psychiatric Association, 2000). This is problematic in the diagnosis of children because irritability is considered a modified feature of a major depressive episode for children, as well as an associated feature of various other psychiatric disorders of childhood such ADHD, oppositional defiant disorder (ODD), and pervasive developmental disorders (PDD) (Dickstein & Leibenluft, 2006). As a result, the inclusion of irritability when diagnosing BPD in children presents a challenge for professionals to accurately diagnose BPD versus other disorders.

Behavioral profile and pediatric bipolar disorder. Beyond the diagnostic criteria that are a central to a DSM-IV-TR diagnosis of BPD, children often present with additional behavioral problems that complicate diagnosis. Broad band behavioral assessment tools, such as the Achenbach Child Behavior Check List (CBCL)(Achenbach, 1991), may be useful to researchers and clinicians by examining a wide range of behavioral issues that can be helpful in furthering our understanding of BPD diagnosis. The CBCL is a well-studied, psychometrically sound behavioral checklist that relies on parent or teacher report (Achenbach, 1991; Achenbach & Edelbrock, 1983) and can be used to build a profile of behavior that encompasses primary BPD diagnostic criteria, comorbid diagnostic criteria and additional non-diagnostic, but related features.

Utilizing this checklist, a number of researchers have identified a CBCL behavioral profile for children diagnosed with BPD (Biederman, et al., 1995; Faraone, Althoff, Hudziak, Monuteaux, & Biederman, 2005; Geller, Warner, Williams, Zimerman, 1998; Giles, DelBello, Stanford, & Strakowski, 2006; Mick, Biederman, Pandina, & Faraone, 2003). Biederman et al. (1995) was the first to identify a profile specific to mania, which includes clinically significant elevation on the following subscales: Attention Problems, Aggressive Behavior, and Anxious/Depressed syndrome scales. This has been replicated by other researchers in similar samples (Biederman, et al., 1995; Faraone, et al., 2005; Mick, et al., 2003), across age groups (Gabrielle A. Carlson & Kelly, 1999; Geller, Warner, Williams, & Zimerman, 1998), and across cultures (American, Dutch, Brazilian, Australian) (Boomsma, et al., 2006; Faraone, et al., 2005). This profile can distinguish children with BPD from children with other psychological disorders, such as depression, ADHD, and other disruptive behavioral disorders, which

all share some diagnostic criteria (Biederman, et al., 1995; Kahana, Youngstrom, Findling, & Calabrese, 2003). As such, this profile may be useful for refining the assessment of psychopathology, and may improve accuracy in diagnosing BPD in children.

Neuroanatomy and bipolar disorder. Technological advances in brain imaging, such as magnetic resonance imaging (MRI), have allowed more extensive examination of the neurological basis of BPD in both adults and children. The medial temporal lobe has been of particular interest due to its role in mood regulation and emotional memory (Martin, 2003). This brain region includes the amygdala, hippocampus, and superior temporal gyrus, which are critically involved in speech, language, learning, memory, and emotion, in addition to mood regulation (Brambilla, Glahn, Balestrieri, & Soares, 2005; Sweeten, Posey, Shekhar, & McDougle, 2002). Specifically, the amygdala is responsible for the production of symptoms such as fear, anxiety, and dysphoria, the regulation of emotional responses, and in the formation and storage of emotional memory (Brambilla, et al., 2005). The hippocampus is involved in learning, memory, mood, and behavior.

The use of MRI to study BPD in adults has resulted in some noteworthy, yet inconsistent findings. The volume of the temporal cortex has been reported to be larger (Harvey, Persaud, Ron, & Baker, 1994) or not different (Hauser, et al., 2000) in adults with BPD compared to controls. The volume of the amygdala has been reported to be larger bilaterally (Altshuler, et al., 2000; Strakowski, et al., 1999) or smaller in the left hemisphere (Pearlson, et al., 1997) in samples of adults with BPD compared to controls. In mixed aged samples, however, the amygdala has been reported to be smaller bilaterally (Blumberg, et al., 2003), or not different (Chen, et al., 2004; Hauser, et al.,

2000) compared to controls. In addition, the volume of the hippocampus is typically reported not to differ between samples of adults (Altshuler, et al., 2000) or mixed aged-samples (Blumberg, et al., 2003; Chen, et al., 2004) with BPD compared to similarly aged controls. These studies suggest that differences in brain structure volumes in persons diagnosed with BPD relative to controls may vary by age.

There are very few neuroimaging studies that examine brain volumes exclusively in children with BPD. The left amygdala was reported to be significantly smaller in children with BPD compared to controls (Dickstein, et al., 2005). Similarly, in another study, the left temporal cortex and the left superior temporal gyrus was significantly smaller in children with BPD compared to controls (Frazier, et al., 2005). However, the only published study, of which I am aware, examining hippocampal volume in a purely pediatric sample of BPD individuals reported no differences in hippocampus volume between children with and without a BPD diagnosis (Dickstein, et al., 2005). Thus, although the literature on adults with BPD is inconsistent, the few studies that specifically address pediatric BPD provide some evidence for smaller left temporal structures compared to controls (Dickstein, et al., 2005; Frazier, et al., 2005).

In summary, a behavioral profile of pediatric BPD has been identified and replicated, and a pattern of smaller temporal cortex structure volumes has been noted. Still, diagnostic controversy continues to exist, in part, due to the overlap between the diagnostic profiles of pediatric BPD and other pathological conditions of childhood. Thus, additional research is needed to clarify the complex nature of pediatric BPD and improve its diagnosis. This is an important problem given the profound implications of diagnosis for children and their families.

Autism Spectrum Disorders

According to the DSM-IV-TR, Autistic Disorder has an onset prior to age three and falls under the larger heading of Pervasive Developmental Disorders (American Psychiatric Association, 2000). It is characterized by the following primary diagnostic criteria: (1) qualitative impairment in social interaction, (2) qualitative impairment in communication, and (3) restricted repetitive and stereotyped patterns of behavior, interests, and activities (American Psychiatric Association, 2000). In addition, autistic disorder is commonly associated with other features, including abnormalities in eating, a lack of fear in response to dangers, abnormalities of affect, as well as self-injurious behaviors (American Psychiatric Association, 2000). Moreover, autistic children are often, but not always, diagnosed with mental retardation ranging from mild to profound (American Psychiatric Association, 2000). Thus, within the diagnosis of autistic disorder, the symptoms and severity of symptoms vary between individuals.

Similar to pediatric BPD, diagnosis of autistic disorder is surrounded by controversy; however, the nature of the controversy is quite different. What was once thought of as a single disorder is now thought of as a spectrum of similar disorders that vary mostly in degree. Autism, as well as Asperger's Syndrome and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), is now considered one of several Autism Spectrum Disorders (ASD) (Shriver, 2008). Thus, due to the variability in presentation of autistic disorder, as well as the additional heterogeneity stemming from similarities and overlapping diagnostic criteria related to Asperger's Syndrome and PDD-NOS, researchers and clinicians have found it difficult to accurately diagnosis and identify effective treatments and causal factors in this population.

In recent years, autism has also been in the public eye due to concern over an apparent increase in its prevalence. In the 1980's and 1990's, three of four US population-based studies identified a prevalence rate for autistic disorder of approximately 4 per 10,000 children (Bertrand, et al., 2001; Burd, Fisher, & Kerbeshian, 1987; Kirby, Brewster, Canino, & Pavin, 1995; Ritvo, 1989). More recently, studies have reported the rate to be closer to 3 or 4 children per 1,000 (Bertrand, et al., 2001; Yeargin-Allsopp, et al., 2003). Moreover, in 2007, the Centers for Disease Control and Prevention (CDC) estimated an even higher prevalence (1 in 150) when the entire spectrum of autistic disorders was considered (Department of Health and Human Services, 2007). Researchers and professionals have hotly debated this rise in prevalence; many attribute the dramatic rise in prevalence to symptom substitution, or reclassification of children from one diagnostic category to another (Croen, 2002; Shattuck, 2006). In fact, while the prevalence of autism has increased in recent years, the prevalence of mental retardation and learning disabilities has decreased (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2005; Shattuck, 2006). This phenomenon may be the result of the shifting and expanding of the diagnostic criteria for autistic disorder, as well as changing referral practices.

As a result of these and other controversies surrounding ASDs, as well as the significant impact this diagnosis can have on families and on society as a whole, there has been a push in recent years to identify the etiology of the disorder and develop services for children with ASDs and their families. Specifically, Federal and State legislation has been passed to address the prevalence of autism, and, in 2006, President George W. Bush passed the Combating Autism Act of 2006, which allocated money to increase public

awareness and support research and treatment of autism (http://www.whitehouse.gov/news/releases/2006/12/20061219-3.html).

Behavioral profile and autism spectrum disorders. The behavioral profile of children with autism has been examined utilizing the CBCL, although not extensively. In a sample of 204 preschool boys with a variety of psychiatric and developmental disorders, Rescorla (1988)conducted a factor analysis with CBCL items and identified eight factors, one which was named the "Autistic/Bizarre" factor. This factor included items from five different subscales from the CBCL (Confused, Repeated Acts, Strange Behavior, Strange Ideas, Withdrawn).

Another study examined the use of the CBCL for differentiating children with autism from children with other psychiatric disorders or those without diagnosis (Duarte, Bordin, Oliveira, & Bird, 2003). Similar to Rescorla (1988), the Autistic/Bizarre scale significantly distinguished autistic children from control children; however, the Thought Problems subscale of the CBCL was even more accurate at differentiating these children. Interestingly, the Autistic/Bizarre scale also accurately distinguished autistic children from children with various other psychiatric disorders (Duarte, et al., 2003). To the best of my knowledge, these are the only two studies that have used the CBCL to identify a behavioral profile of ASD that goes beyond the traditional DSM-IV-TR diagnostic profile.

In addition, one study examined CBCL scores of children with autism in relation to control and clinical samples. This study reported that the 'total problems' score of the CBCL was able to distinguish children with autism from controls (Bolte, Dickhut, & Poustka, 1999). More specifically, they found that children with autism scored

significantly higher than controls on all but one of the syndrome subscales (somatic complaints)(Bolte, et al., 1999). In addition, compared to a clinical group, autistic children were found to score significantly higher on the social problems, thought problems and attention problem syndrome subscales (Bolte, et al., 1999).

Neuroanatomy and autism spectrum disorders. Much research has demonstrated global neuroanatomical differences between autistic individuals and controls, although these differences vary across the lifespan. Specifically, the literature indicates that "the early childhood period of excessive growth [in autism] is replaced some time during middle to late childhood by a period of relatively slowed growth in the brain overall, as well as the cerebrum, cerebellum, and limbic system" (Courchesne, Redcay, & Kennedy, 2004). Thus, consideration of the age range of an autistic sample is important, and characterization of volumetric differences specifically in children may be critical.

Indirect evidence and postmortem analyses of cellular abnormalities in individuals with an ASD support the involvement of temporal lobe structures, such as the amygdala and hippocampus, in the symptomology and diagnostic features of ASDs (Bauman, 2005). However, reports of volumetric changes in the amygdala and hippocampus of individuals with an ASD are mixed. Some studies have found larger amygdala volumes in those with autism compared to control samples (Howard, et al., 2000; Schumann, et al., 2004; Sparks, et al., 2002), while others have found smaller amygdala volume (Aylward, et al., 1999; Pierce & Courchesne, 2001) or no differences (Haznedar, et al., 2000) compared to controls. Still others have reported larger left amygdala volume in autistic individuals compared to controls (Abell, et al., 1999). Hippocampal abnormality reports have also been inconsistent in the autism literature. The

volume of the hippocampus has been reported by some to be smaller in those with autism compared to controls (Aylward, et al., 1999), while others have found the hippocampus volume larger (Schumann, et al., 2004; Sparks, et al., 2002) or not different between autistic participants and controls (Haznedar, et al., 2000; Piven, Bailey, Ranson, & Arndt, 1998). Finally, there have been some reports of whole temporal lobe volumetric enlargements in autistic individuals (Piven, Arndt, Bailey, & Andreasen, 1996). Overall, research indicates that the medial temporal lobe may be affected by the existence of an ASD (Piven, et al., 1996).

A number of factors may contribute to the variability in these results. Similar to the studies of BPD, neuroanatomical studies of autistic individuals often include a wide age range of participants. Even when researchers statistically control for age effects in their analysis, interpreting the effects of age on volumetric outcomes remains difficult partially due to the non-linear growth pattern of brain structures throughout development. Many studies also include autistic individuals with wide ranging IQ scores or individuals that fall on the broader autism spectrum. Therefore, it becomes a challenge to tease apart the abnormalities associated with IQ differences as opposed to differences specifically associated with autism.

By definition, there is a large amount of variability within the classification of autism spectrum disorder making it difficult to ascertain behavioral and neuroanatomical correlates to this disorder. With a general perception of an increasing prevalence there has been a great deal of research directed at better understanding ASDs. While advances have been made, leading to a more widely accepted and recognized diagnosis, more

research is needed to understand the influence of the many psychopathological conditions that often co-occur among individuals with ASDs.

Comorbid Disorders & Latent Class Analysis

Although BPD and ASD are markedly different disorders, there is extensive variability in the presentation within each disorder. Comorbidity may be a potentially important contributor to this variability. For example, ADHD (Wozniak, et al., 1995) and anxiety disorders (Dickstein, et al., 2005) often co-occur with BPD. Social anxiety disorder, ADHD, and ODD are the most common comorbid diagnoses in children with ASD (Simonoff, et al., 2008). One study reported that 70% of those with ASD had at least one comorbid disorder, and 41% had two or more (Simonoff, et al., 2008); however the presence and rate of comorbidity in those with ASDs requires more study (Matson & Nebel-Schwalm, 2006).

The DSM-IV-TR specifically states that because it uses a categorical classification system for diagnosis and is based on criteria sets with defining features (rather than etiology), heterogeneity within diagnosis as well as overlap with other diagnoses may be widespread (American Psychiatric Association, 2000).

> In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. The clinician…should therefore consider that individuals sharing a diagnosis are likely to be heterogeneous even in regard to the defining features of the diagnosis and that boundary cases will be difficult to diagnose in any but a probabilistic fashion (American Psychiatric Association, 1994, pg. xxii).

In summary, the presence of comorbidity makes it difficult to identify the neuroanatomical correlates and accurately capture the distinctive behavioral features of a

given diagnosis (Matson & Nebel-Schwalm, 2006). As a result, it is important to consider comorbidity when studying these disorders. To date, most neuropsychological, neuroanatomical and behavioral research focuses on primary BPD or ASD diagnoses only, often not reporting or accounting for the potentially considerable influence of comorbid conditions.

Person-centered statistical techniques, such as latent class analysis (LCA), attempt to make sense of the complexities in the patterns of interacting variables to more fully characterize the individual (Bates, 2000; Magnusson, 1998). Using a sample of children, ages 7 -13 years old, with a primary diagnosis of ASD or BPD, an IQ >70, and an LCA approach, this study seeks to identify empirically-derived diagnostic groups that take into account a wide variety of childhood psychopathological conditions. In other words, the aim is to create more homogeneous diagnostic classes by considering diagnoses of ASD and BD together with diagnoses of disruptive behavior disorder, attention-deficit hyperactivity disorder, depression, and anxiety. Subsequently, traditional variable-centered approaches are used to better understand both the behavioral presentation and the brain structural abnormalities of these classes of individuals.

The Current Study

The current study aims to utilize comorbid diagnostic information to better characterize children with a primary diagnosis of ASD or BPD, and further, to identify clearer distinctions in terms of behavior and structural neuroanatomical features of the temporal lobe. Using a sample of 112 children, ages 7 -13 years old, with a primary diagnosis of ASD or BPD, and an IQ >70, this study seeks to identify empirically-derived diagnostic groups that take into account a wide variety of childhood psychopathological

conditions. A person-centered statistical technique, latent class analysis (LCA) will be utilized in an attempt to create empirical groups of children who are less variable in behavioral symptoms and temporal cortex brain structure volumes than those grouped by primary diagnosis (ASD/BPD) alone. Person-oriented analytic approaches are generally exploratory and better equipped to detect salient patterns in data that represent multidimensional and interactional relationships than variable-oriented approaches such as regression analysis (Bates, 2000; Magnusson, 1998). The behavior profiles and neuroanatomical features of the temporal lobe of the resultant clinical groups will be compared, and also contrasted to those of 27 healthy controls.

Specifically, the hypotheses of the current study were:

1. With a broader array of comorbid diagnostic information, more homogenous groups, based on a pattern of diagnostic categories of psychopathology, will be empirically identified using LCA, compared to grouping based on DSM based diagnostic classifications (ASD/BPD). It is expected that resulting groups will reflect two or more primary diagnostic classes with different patterns of comorbidity.

2. Behavioral profiles will be different across diagnostic groups based on DSM diagnosis. Differences in behavioral profiles between classes may be more pronounced if an empirically identified class encompasses more substantial levels of comorbidity compared to the other classes. Children with ASD will score significantly more often in the clinically impaired range on the Thought Problems subscale on the Child Behavior Checklist (Achenbach, 1991) compared to the BPD and control groups, using a classification system based on primary DSM based diagnosis alone. Similarly, children diagnosed with BPD will score significantly more often in the clinically impaired range

on the Aggressive Behavior, Attention Problems, and Anxiety Depression subscales compared to the other groups, consistent with Biederman et al,'s (1995) findings.

3. Neuroanatomical profiles will be different across the empirically identified groups based on a high probability of latent class membership. To date, studies examining the structural volumes of the temporal lobes in healthy children and those diagnosed with ASD or BPD have been inconsistent. In this study, by utilizing a LCA approach and analyzing comorbid diagnostic disorders in LCA, we expect to see less variability within each group, and thus may be better positioned to identify group differences in brain volumes. Specifically, it is hypothesized that classes with highest comorbidity will deviate the most from the control group.

CHAPTER II

Methods

Participants and Clinical Diagnosis

This study includes 112 children with a primary diagnosis of either an ASD (*n* = 69 boys; 7 girls) or BPD (*n* = 26 boys; 10 girls) recruited from a university hospital, and 27 healthy controls (19 boys; 8 girls) (see the Procedure section for greater detail). The ASD group included 19 individuals with high-functioning autism (Autistic Disorder) and 57 with Asperger's Disorder. Diagnosis for an ASD was based on the Schedule for Affective Disorders and Schizophrenia for School Age Children, the Present State and Epidemiological Version (K-SADS-IVR) (Ambrosini & Dixon, 1996), a semi-structured clinical interview created from a checklist for the criteria of Autism and Asperger's Syndrome based on the Diagnostic and Statistical Manual-IV (DSM-IV) (American Psychiatric Association, 1994), and the Autism Diagnostic Interview-Revised (ADI-R, (Lord, Rutter, & Le Couteur, 1994)). Diagnosis of BPD was based on the K-SADS-IVR. All participants were also assessed for other DSM-III diagnoses with the K-SADS_IVR (see M-Table 1).

M-Table 1
Latent Class Analysis Labels and Number of Diagnoses from the K-SADS

	Reduced Categories for LCA	*ASD**	*BPD**
Attention Deficit Hyperactivity Disorder	ADHD	10/7	2/6
Inattentive Type			
Hyperactive Type	ADHD	5/3	1/0
Combination	ADHD	15/25	3/22
Asperger's Disorder	PDD	0/56	1/0
High Functioning Autism	PDD	0/20	1/0
Bipolar I	BPD	3/6	0/27
Bipolar II	BPD	8/4	0/9
Major Depressive Disorder	Depression	6/3	3/15
Minor Depression	Depression	10/3	6/4
Dysthymia	Depression	8/3	3/2

Continued -- M-Table 1 Latent Class Analysis Labels and Number of Diagnoses from the K-SADS

Depressive Disorder – Not Otherwise Specified	Depression	1/0	0/0
Avoidant Disorder	Anxiety	11/8	3/0
Generalized Anxiety Disorder	Anxiety	8/17	6/9
Overanxious Disorder	Anxiety	14/10	14/11
Post-Traumatic Stress Disorder	Anxiety	0/0	1/1
Panic Disorder	Anxiety	0/0	0/1
Separation Anxiety	Anxiety	2/3	3/2
Specific Phobia	Anxiety	12/22	9/11
Social Phobia	Anxiety	2/3	1/1
Obsessive Compulsive Disorder	Anxiety	13/40	5/5
Anxiety Disorder – Not Otherwise Specified	Anxiety	0/1	0/0
Oppositional Defiant Disorder	Disruptive Behavior Disorder	23/8	13/20
Conduct Disorder	Disruptive Behavior Disorder	1/0	2/5

Continued -- M-Table 1 Latent Class Analysis Labels and Number of Diagnoses from the K-SADS

Eating Disorder – Not Otherwise Specified	--	0/1	0/1
Schizotypal	Schizophrenia Spectrum Disorders	3/0	4/0
Schizophrenia	Schizophrenia Spectrum Disorders	11/0	4/2
Schizoaffective Disorder	Schizophrenia Spectrum Disorders	4/0	5/2
Pica	--	0/1	0/0
Tourette's Disorder	--	0/1	0/0
Trichotillomania	--	0/1	0/0
Dissociative Disorder– Not Otherwise Specified	--	0/0	0/1

**Number of participants with a Subthreshold/Threshold Diagnosis*

The mean age of the overall sample was 9.92 years of age (range 7 – 13 years). The average full-scale IQ from the Wechsler Intelligence Scale for Children-Third Edition (Wechsler, 1991) was 99.71; individuals with a full-scale IQ below 70 were excluded from this study. Exclusion criteria also included a current medical illnesses, central nervous system diseases, or learning disabilities. Participants were also excluded if the MRI was contraindicated or refused. Due to ethical concerns regarding withholding treatment, children who were taking psychotropic medications continued; however, no new medications were initiated during the study. The most common classes of medication being taken were psychostimulants, mood stabilizers, and antidepressants. None of the participants in the Control group were taking any medication at the time of the evaluation. Missing observations were mostly due to parents' and/or teachers' inability or unwillingness to complete behavioral measures (CBCL or TRF), or because the MRI could not be read due to movement artifacts, obscured boundaries, or other MRI resolution difficulties. No participants were dropped from the sample and missing data was handled in SAS version 9.1.

Procedure

Clinical participants were recruited from the outpatient, inpatient, and day programs of a university medical center in the Northeastern United States. Participants in the healthy control group were recruited by word of mouth and from local pediatric offices. Following recruitment and an initial telephone screening interview, interested parents were scheduled for an in-person interview, during which they received a thorough explanation of the project and completed informed consent and assent procedures. All parents were then administered the K-SADS-IVR by a trained clinician, while the

children completed a neuropsychological testing battery. In addition, parents were also asked to fill out the Achenbach Child Behavior Checklist (CBCL) (Achenbach, 1991), and the Achenbach Teacher Report Form (TRF) was also sent home to be completed by the child's teacher. Children were then scheduled for the MRI within usually two weeks of the initial interview. In order to allow the children and parents to become familiar with the imaging process, families were given a video which showed the sequence of procedures they would experience at the imaging center. Clinical participants received a written neuropsychological report and the control participants were reimbursed $100.00 in lieu of the neuropsychological report. The study was approved by the Institutional Review Boards of Rutgers University and UMDNJ-Robert Wood Johnson Medical School.

Behavioral Measures

Achenbach child behavior check list (CBCL). The CBCL (Achenbach, 1991)is a well-studied, psychometrically sound behavioral checklist used to obtain parent report of their child's (ages 4-18) competencies and problem behavior (Achenbach, 1991; Achenbach & Edelbrock, 1983). This parent-report measure yields eight syndrome scales: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior. Two broad band scales are also calculated: Internalizing Behavior Problems and Externalizing Behavior Problems. The Internalizing Behavior Problems subscale is composed of the Withdrawn, Somatic Complaints, Anxious/Depressed syndrome scales, and the Externalizing Behavior Problems subscale is composed of the Delinquent Behavior and Aggressive Behavior syndrome scales.

Achenbach teacher report form (TRF). The Achenbach TRF (Achenbach, 1991) is a widely used behavioral checklist reported by a teacher of a child (ages 5-18) (Achenbach, 1991; Achenbach & Edelbrock, 1983). The TRF produces the same narrow band and broad band scale scores as the parent report CBCL. This measure was mailed to the participants' teachers.

Neuroanatomy: Amygdala, Hippocampus, and Temporal Lobe

MRI acquisition. Magnetic Resonance Imaging (MRI) scans were acquired on a high field strength (1.5 Tesla) General Electric Clinical Scanner located at the Laurie Imaging Center (New Brunswick, NJ). A coronal series of 124 contiguous 1.5mm thick, 0-gap, T-1 weighted SPGR (spoiled grass) images (VBw, EDR, FAST, Irp, TR 25ms TE 5ms, T1/Flip 40, Bandwith 16.0, FOV 24, 256*192 matrix), were obtained. No sedation was administered prior to the MRI scan, and either one parent or investigator remained with the child throughout the scan to provide reassurance, promote cooperation, and assure image quality. Each MRI scan took 10 minutes 18 seconds.

Volumetric analysis. Following the completion of the scan, the imaging data were transferred to the laboratory for post-processing. Next, the imaging files were converted from a diacom format to an AVW format, and the amygdala, hippocampus, and temporal cortex were analyzed utilizing AnalyzePC software (Robb, 2001).

Amygdala segmentation. Image files were converted to cubic voxel dimensions of 0.469 mm using a cubic spline interpolation algorithm. Then, the files were reoriented to align along a horizontal axis from the rostral tip to the caudal extent of the amygdala. The tracing protocol of the amygdala included initially defining the structure in coronal sections beginning with the most caudal section. The borders of the amygdala were

defined laterally and ventrally by the adjacent white matter, medially and dorsally by the medial surface of the brain, and ventromedially by the alveus. The amygdala boundaries were further demarcated by the surrounding gray matter structures. Furthermore, accuracy was ensured by checking the tracing in the axial and sagittal views as well. The structure of the amygdala was traced by one rater who was blind to the diagnosis of the subject. This rater established a high intra-rater reliability correlation ($r>.95$). A more detailed explanation of the amygdala segmentation process can be found in Schumann et al. (2004).

Hippocampus segmentation. For hippocampus segmentation, image files were converted to 0.938 mm slice thickness. The structure was segmented so that the horizontal axis could be drawn from the rostral tip to the caudal extent of the hippocampus in the coronal plane. The medial boundary of the structure was defined by a band of white matter between the retrosplenial cortex and the hippocampus, and the fornix served as the dorsomedial and lateral boundary of the structure. In the most caudal section of the hippocampus, a white matter tract of the temporal cortex served as the ventral boundary; and in the more rostral sections, the alveus, temporal horn of the lateral ventricle, entorhinal cortex, and white matter of the temporal cortex were used as boundaries. The structure of the hippocampus was traced by one rater who was blind to the diagnosis of the subject. This rater established a high intra-rater reliability correlation ($r>.96$). A more detailed explanation of the hippocampus segmentation process utilized can be found in Schumann et al. (2004).

Temporal segmentation. For the purposes of segmenting the temporal lobe, a 2 mm slice thickness was used. The structure was segmented in the coronal orientation and

was traced posterially. The superior boundary of the structure was defined by the Sylvian fissure; the lateral boundary the superior and medial temporal gyri; and the medial boundary the inferior temporal gyrus. The left and right temporal cortexes were traced separately, based on a prior established protocol (Bryant, Buchanan, Vladar, Breier, & Rothman, 1999; Hosoya, Adachi, Yamaguchi, & Haku, 1998). The temporal lobes were traced by two raters, who established both high intra-rater reliability (Rater 1 Right Temporal Lobe ICC= .96; Rater 1 Left Temporal Lobe ICC= .90; Rater 2 Right Temporal Lobe ICC= .95; Rater 2 Left Temporal Lobe ICC=.90) and inter-rater reliability (Right Temporal Lobe ICC= .87; Left Temporal Lobe ICC= .92).

Analyses

Latent Class Analysis (LCA) was used to identify mutually exclusive, homogeneous groups (classes) of individuals based on the *pattern* (McCutcheon, 1987) of their diagnostic symptoms and performed using MPlus (Muthén, 1998-2006). LCA is based on the conditional independence assumption that with the unobserved latent classes taken into account, patterns of endorsement probabilities for each diagnostic criterion included in LCA are independent. The probabilities of a given individual meeting a given diagnostic criterion and of belonging to a specific latent class (based on the similarity of an individual's support profile to the class profile) were computed.

In line with the present hypotheses, individuals were categorized as 0 = absence or 1 = presence for each of diagnostic symptoms at the sub-threshold level, even if they did not meet full criteria for a diagnosis. This strategy enabled us to account for individuals who presented with clinically significant problems that might have impacted the presentation and course of a primary diagnosis. From the 31 K-SADS-IVR categories,

five disorders (Eating Disorder – Not Otherwise Specified, Pica, Tourette's Disorder, Trichotillomania, and Dissociative Disorder – Not Otherwise Specified) were removed because symptoms and diagnosis were very rare. Based on DSM-IV-TR categorization of disorders, the remaining 26 diagnoses were consolidated into six diagnostic categories (M-Table 1). LCA models were examined using these seven binary diagnostic indices with missing data assumed to be missing at random and ignorable (Little, 1987).

An initial model with one class was specified, with each additional class added to the model in a stepwise fashion. The optimal number of classes was determined by comparing the goodness of fit statistics, including Bayesian Information Criterion (BIC) and entropy, as well as interpretability of classes based on the literature.

Following identification of the classes, differences in behavioral profile (from the CBCL and the TRF) and brain structure volumes (amygdala, hippocampus, temporal cortex) were compared across the resulting classes. Significant group differences were examined within the SAS environment using analysis of covariance (ANCOVA) by assigning individuals to a latent class based on their most probable membership. For the behavioral profile analyses, age and gender were included as covariates. For the brain structural volumes, total brain volume was entered into the model as a covariate to adjust for age-related differences. In addition to statistical assessments, the usefulness of the latent class approach for increasing within-group homogeneity in behavioral profile scores and/or structural volumes was characterized descriptively using scatterplots.

CHAPTER III

Results

Primary Diagnosis

The primary goal of this dissertation was to explore a person-centered analytic approach to classify children with psychopathology using primary and comorbid diagnostic information in an effort to empirically identify groups that are more homogeneous within groups but maximally different from others. In addition, this dissertation examined distinctive patterns of neuroanatomical and behavioral profiles (as perceived by parents and teachers) that are associated with the newly identified groups. Initially, children were categorized based on their primary diagnoses, either an ASD or BPD, defined in terms of standard criteria K-SADS and DSM-IV criteria. CBCL/TRF behavioral profiles and MRI volumetric data were then compared between the ASD and BPD groups as well as to control children, who did not meet criteria for a primary psychopathology diagnosis.

Behavioral Profiles Reported by Parents

Controlling for age and gender, children diagnosed with a primary ASD or BPD diagnosis differed from children in the control group in behavior problems and competencies measured using parent-report Child Behavior Checklist. As in Table 1., both the ASD and BPD groups differed from the control group on every subscale of the CBCL, except the Activities subscale. Behavioral profiles of the three groups are graphically displayed in Figure 1. In addition, the ASD group scored significantly lower

on the Activities subscale than controls and the ASD and BPD groups both scored significantly lower than controls on two measures of Parent-Reported Competence: Social competence, which measures social interaction patterns, and School competence, which measures the presence/absence of parent-reported school competence.

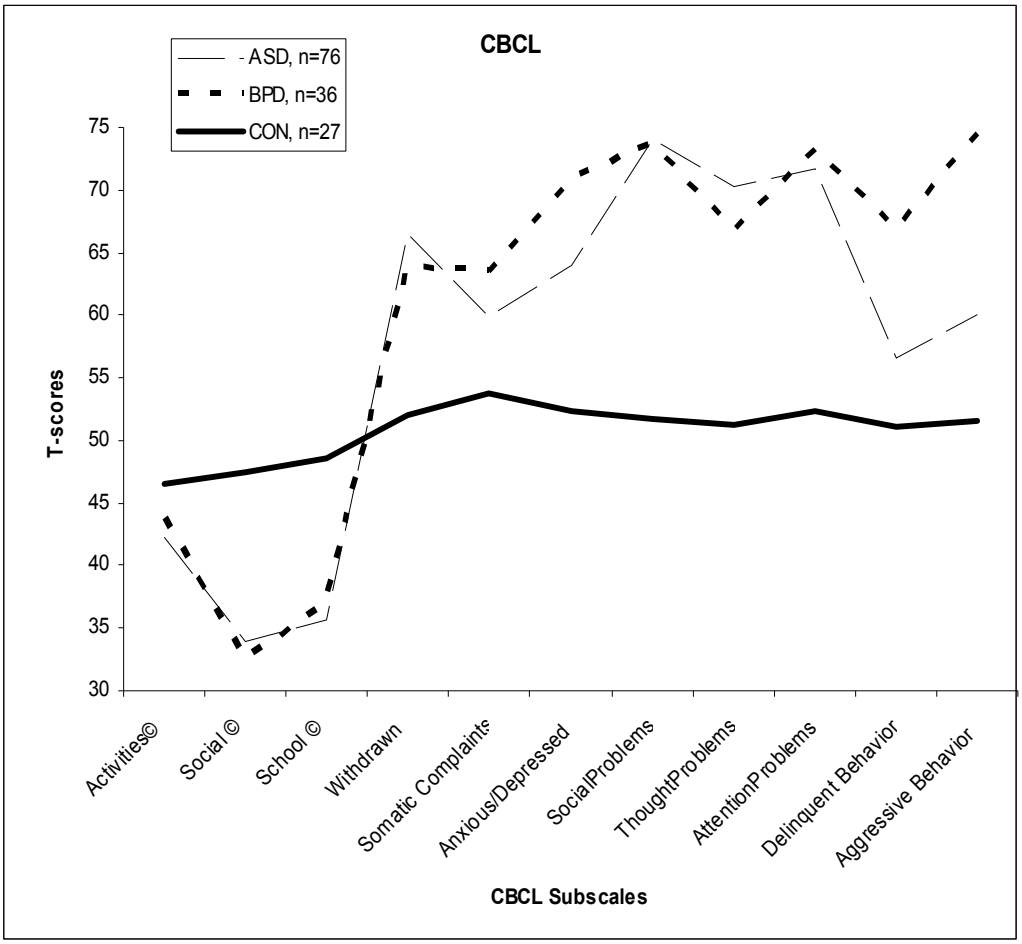

Figure 1. Behavior profiles based on parent-report CBCL

Notes. ASD = Autism Spectrum Disorder; BPD = Bipolar Disorder; CON = Control; CBCL = Achenbach Child Behavior Checklist; ©=Parent-Reported Competence Scale

Figure 1 also illustrates a general pattern of problem behaviors and competencies in the ASD and BPD groups, with both groups reaching clinically significant levels of problem behavior (T-score >70; age and gender normative T-score mean = 50) and parent-reported competencies (T-score > 30 age and gender normative) on several subscales. Specifically, parents of children in the ASD group reported clinically significant levels of perceived problem behavior on the Social Problems and Attention Problems subscales, as well as the Thought Problems subscale which previously has been found to accurately differentiate children with ASD from healthy controls. It is important to note that although the subscales that comprised Biederman et al.'s (1995) profile were not exclusively elevated in this sample, parents of children in the BPD group reported clinically significant levels of perceived problem behavior on the subscales Biederman et al. (1995) identified in his profile: Anxious/Depressed, Attention Problems, and Aggressive Behavior subscales. The Social Problems subscale also fell into the clinically significant range. The BPD group also demonstrated significantly greater Anxious/Depressed, Delinquent Behavior, and Aggressive Behavior scores compared to the ASD group (Table 1).

Table 1
Descriptive Statistics (Adjusted Mean [controlling for Gender and Age] ± Standard Error) for CBCL-Parent Variables

CBCL-Parent Variables (T-scores)	*ASD*	*ASD n*	*BPD*	*BPD n*	*CON*	*CON n*	
Activities ©	42.32 ± 0.93	68	43.91 ± 1.44	28	46.59 ± 1.53	*25*	$F(4, 120) = 1.44$, *n.s.*
Social ©	33.88 ± 1.04 [b]	66	32.49 ± 1.53 [b]	30	47.53 ± 1.70	*25*	$F(4, 120) = 13.83$, $p<.05$
School ©	35.72 ± 0.90 [b]	65	37.06 ± 1.34 [b]	29	48.53 ± 1.45	*25*	$F(4, 118) = 14.88$, $p <.05$
Withdrawn	66.52 ± 1.14 [b]	70	63.88 ± 1.70 [b]	31	51.98 ± 1.91	*25*	$F(4, 125) = 11.66$, $p <.05$
Somatic Complaints	59.92 ± 1.08 [b]	70	63.53 ± 1.62 [b]	31	53.72 ± 1.81	*25*	$F(4, 125) = 4.57$, $p <.05$
Anxious/Depressed	63.96 ± 1.16 [a b]	70	70.96 ± 1.75 [b]	31	52.33 ± 1.94	*25*	$F(4, 125) = 13.32$, $p <.05$
Social Problems	74.08 ± 1.12 [b]	70	73.77 ± 1.66 [b]	31	51.67 ± 1.86	*25*	$F(4, 125) = 29.14$, $p <.05$
Thought Problems	70.22 ± 1.04 [b]	70	66.87 ± 1.56 [b]	31	51.31 ± 1.75	*25*	$F(4, 125) = 22.70$, $p <.05$
Attention Problems	71.70 ± 1.02 [b]	70	73.27 ± 1.52 [b]	31	52.30 ± 1.70	*25*	$F(4, 125) = 27.75$, $p <.05$
Delinquent Behavior	56.57 ± 0.93 [a b]	70	67.01 ± 1.40 [b]	31	51.11 ± 1.56	*25*	$F(4, 125) = 16.30$, $p <.05$
Aggressive Behavior	60.06 ± 1.13 [a b]	70	74.57 ± 1.70 [b]	31	51.48 ± 1.90	*25*	$F(4, 125) = 22.54$, $p <.05$

Notes. ASD = Autism Spectrum Disorder; BPD = Bipolar Disorder; CON = Control; CBCL = Achenbach Child Behavior Checklist; ©=Parent-Reported Competence Subscale; [a]= significantly different from BPD; [b]=significantly different from CON

Behavior Profiles Reported by Teachers

In addition to distinctive behavior profiles reported by parents, teachers noted substantial differences between children with a primary diagnosis of ASD or BPD and children in the control group. Figure 2 illustrates that both diagnostic groups displayed a behavior profile with elevated scores on problem behavior subscales and depressed scores on adaptive functioning subscales compared to controls, whose T-scores were fairly stable around the age and gender normative mean across all subscales (range: 50.48-55.78). Specifically, the ASD group scored in the 'at risk' range (T-scores between 67 and 70) on the Thought Problems subscale. They also scored significantly greater than the control group on all problem behavior subscales and significantly lower on all adaptive functioning subscales, except the Working Hard subscale (Table 2.). The BPD group scored in the 'at risk' range on the Anxious/Depressed subscale and received significantly greater scores than the control group on all clinical subscales and significantly lower scores on all adaptive functioning subscales (Table 2.). Although the overall the pattern of perceived behavior by teachers was similar in the two diagnostic groups, teachers reported that children in the BPD group demonstrated significantly greater levels of Anxious/Depressed and Delinquent Behavior compared to the ASD group (Table 2.). The diagnostic group differences on the teacher-reported scores on the Aggressive Behavior subscale did not achieve statistical significance, yet the profile of teacher perceptions on this subscale reflected a similar trend to those reported by parents. In terms of adaptive functioning, the ASD group was perceived by teachers to have significantly greater levels of adaptive functioning on the Happy subscale compared to the BPD group (Figure 2; Table 2.)

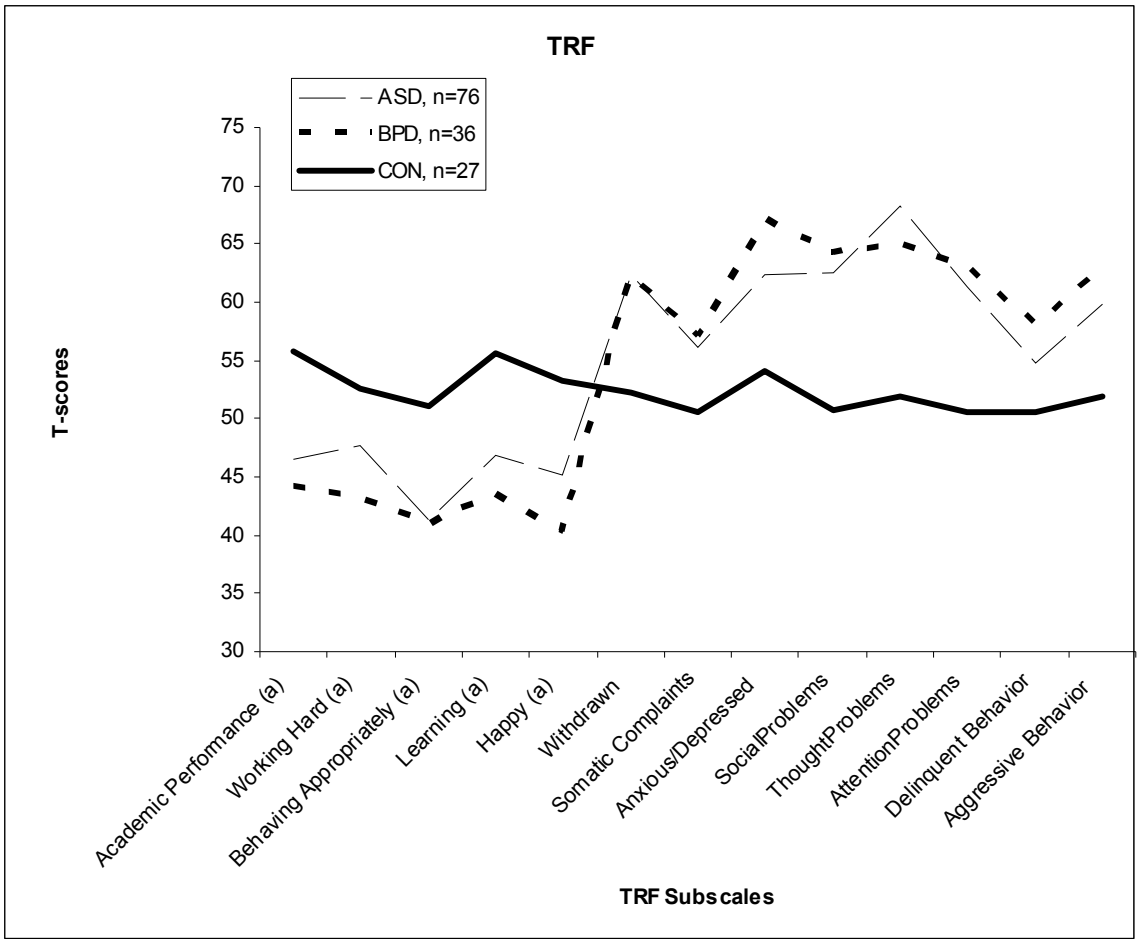

Figure 2. Behavior profiles based on teacher version (TRF) of Achenbach CBCL

Notes. ASD = Autism Spectrum Disorder; BPD = Bipolar Disorder; CON = Control; CBCL = Achenbach Child Behavior Checklist; TRF = Teacher Report Form; (a) =Adaptive Functioning Subscale

Table 2
Descriptive Statistics (Adjusted Mean [controlling for Gender and Age] ± Standard Error) for TRF Variables

TRF-Subscales (T-scores)	*ASD*	*ASD n*	*BPD*	*BPD n*	*CON*	*CON n*	
Academic Performance (a)	46.52 ± 1.11 [b]	55	44.16 ± 1.67 [b]	24	55.78 ± 2.67	*10*	$F(4, 88) = 4.12$, $p<.05$
Working Hard (a)	47.62 ± 1.15	56	43.13 ± 1.84	22	52.63 ± 2.79	*10*	$F(4, 87) = 2.32$, *ns*
Behaving Appropriately (a)	41.25 ± 0.92 [b]	56	40.88 ± 1.43 [b]	23	50.99 ± 2.22	*10*	$F(4, 88) = 6.14$, $p<.05$
Learning (a)	46.84 ± 1.05 [b]	55	43.47 ± 1.66 [b]	22	55.55 ± 2.53	*10*	$F(4, 86) = 4.14$, $p<.05$
Happy (a)	45.25 ± 0.97 [a b]	54	40.20 ± 1.50 [a b]	22	53.18 ± 2.32	*10*	$F(4, 85) = 6.88$, $p<.05$
Withdrawn	62.37 ± 1.17 [b]	57	62.35 ± 1.80 [b]	24	52.27 ± 2.86	*10*	$F(4, 90) = 2.88$, $p<.05$
Somatic Complaints	56.19 ± 1.04 [b]	57	57.08 ± 1.59 [b]	24	50.60 ± 2.54	*10*	$F(4, 90) = 1.32$, *ns*
Anxious/Depressed	62.33 ± 1.12 [a b]	57	67.15 ± 1.71 [b]	24	54.05 ± 2.72	*10*	$F(4, 90) = 4.57$, $p<.05$
Social Problems	62.52 ± 1.13 [b]	57	64.14 ± 1.74 [b]	24	50.79 ± 2.76	*10*	$F(4, 90) = 4.81$, $p<.05$
Thought Problems	68.26 ± 1.25 [b]	57	64.90 ± 1.91 [b]	24	51.98 ± 3.05	*10*	$F(4, 90) = 8.64$, $p<.05$
Attention Problems	61.33 ± 1.10 [b]	57	63.02 ± 1.68 [b]	24	50.48 ± 2.68	*10*	$F(4, 90) = 4.59$, $p<.05$
Delinquent Behavior	54.77 ± 0.79 [a b]	57	58.11 ± 1.21 [b]	24	50.62 ± 1.93	*10*	$F(4, 90) = 3.10$, $p<.05$
Aggressive Behavior	59.83 ± 1.09 [b]	57	63.07 ± 1.66 [b]	24	51.99 ± 2.65	*10*	$F(4, 90) = 3.63$, $p<.05$

Notes. ASD = Autism Spectrum Disorder; BPD = Bipolar Disorder; CON = Control; CBCL = Achenbach Child Behavior Checklist
(a)= Adaptive Functioning Subscale; [a]= significantly different from BPD; [b]=significantly different from CON

Brain Structure Volumes Assessed by Structural MRI

There were no statistically significant mean differences in brain structure volume between the groups on any of the neuroanatomical structures examined (Figure 3 and 4). However, given the small sample sizes and expected low levels of power, effect sizes (ES) were computed by dividing the mean difference between the groups by the pooled standard deviation. ES (*d*) of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (Cohen, 1988). There were small to moderate mean differences between the Control and ASD groups in the temporal cortex volumes (ES = .35). There were also small to moderate mean differences between the Control and BPD groups in the temporal cortex volumes (ES = .32), and amygdala volumes (ES = .38). The BPD group also appeared to have larger hippocampus volumes compared to controls (ES = .51). Although these group differences were statistically non-significant, the observed mean differences in the neuroanatomical structures across the groups that were in the range of small and moderate effect sizes suggest that future studies should assess these structures in larger samples or in samples that are more diagnostically homogeneous**.**

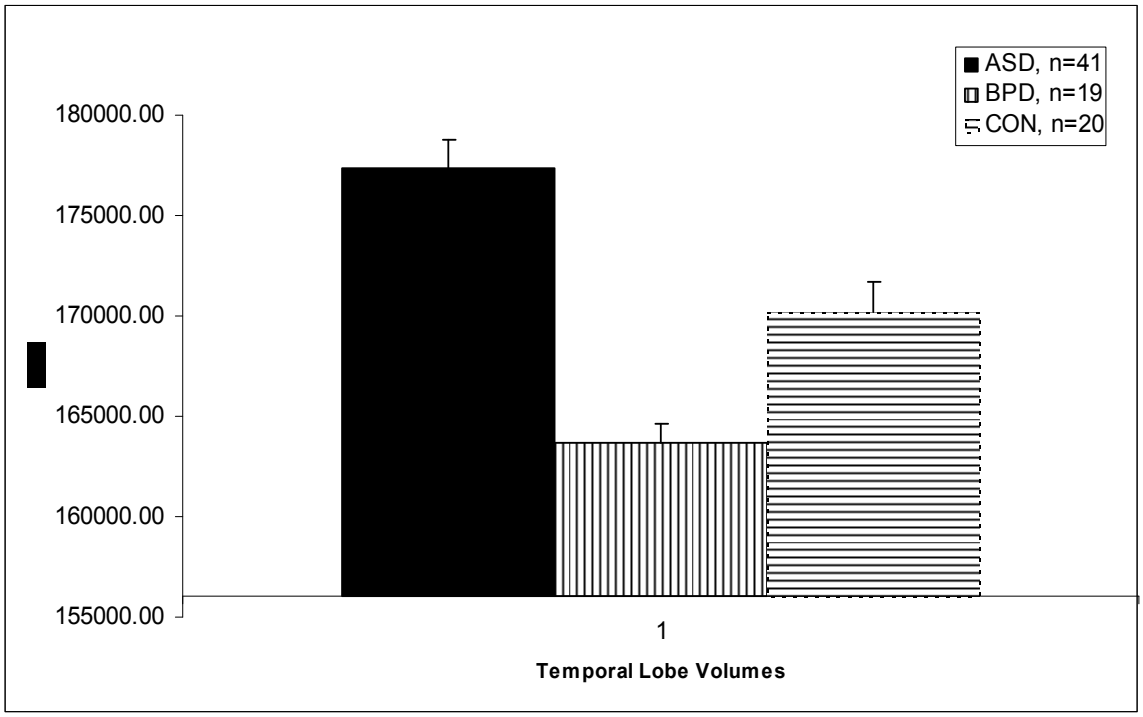

Figure 3. Volumes of total temporal cortex by diagnostic groups

Notes. ASD = Autism Spectrum Disorder; BPD = Bipolar Disorder; CON = Control

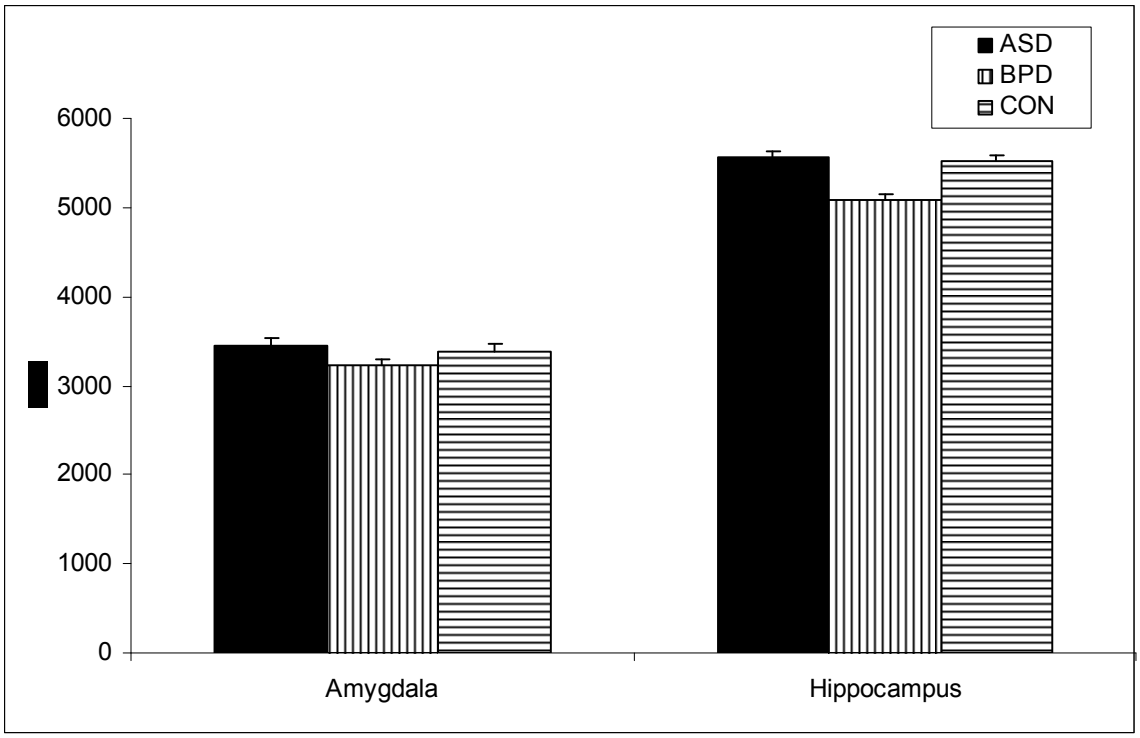

Figure 4. Volumes of amygdala and hippocampus by diagnostic groups

Notes. ASD = Autism Spectrum Disorder (Amygdala, n=22; Hippocampus, n=21);
BPD = Bipolar Disorder (Amygdala, n=14; Hippocampus, n=12);
CON = Control (Amygdala, n=11; Hippocampus, n=11)

Latent Class Analysis

Due to the high levels of comorbidity and variability present within each diagnostic group (ASD and BPD), latent class analysis (LCA) was utilized to explore whether empirically classified groups could provide a better understanding of the link between behavior problems and brain structures. Using data from the children with a primary diagnosis of ASD or BPD, latent class models were fitted to six binary diagnostic categories, including threshold and sub-threshold levels of Attention Deficit Hyperactivity Disorder (ADHD), Disruptive Behavior Disorder (DBD), Pervasive Developmental Disorder (PDD), Bipolar Disorder (BPD), Depression, and Anxiety Disorder. Diagnoses of schizophrenia were excluded from the LCA due to low overall prevalence of this diagnosis in the sample. Data from 112 children who were clinically diagnosed with a primary ASD or BPD were subjected to LCA. There was extensive comorbidity present in the sample, and several children received diagnosis of an ASD and BPD. Overall, threshold and sub-threshold levels of ADHD was present in 88% of the sample, Disruptive Behavior Disorder was present in 58%, PDD was present in 70%, BPD was present in 51%, Depression was present in 60%, and Anxiety Disorder was present in 88% of the sample. Control children were not included in the LCA because children who met criteria for any clinical diagnosis were excluded from the control group. Thus, to allow comparisons of the latent classes to the control group, children with clinical diagnoses were assigned to observable groups based on their most probable class membership. Classes were then compared to control children on all outcome variables using SAS version 9.1.

Fit statistics were compared between LCA models that contained one to five classes (Table 3). A two-class solution was the best-fitting model based on BIC and its ability to identify well-differentiated classes. In the two-class solution, an individual who had been clinically diagnosed with ASD but who also met criteria for four or more comorbid diagnoses, had a high probability of being classified with individuals with BPD (*Comorbid -PDD*, Figure 5). In the three-class model, however, those individuals with ASD, but who also demonstrated four or more comorbid diagnostic conditions, shifted into a distinct highly comorbid class (*Comorbid* Class, Figure 6). Nonetheless, examination of Figures 5 and 6 revealed striking similarities in class profiles of diagnoses, suggesting that the added third class in the three-class model (3 Class solution; Figure 6) did not help explain the heterogeneity in the data better than the two-class model. Therefore, the 2-class solution was selected and the earlier analyses across the diagnostic groups were repeated. The three-class solution was also examined to determine whether it better captured the theoretical influence of comorbidity on diagnosis.

Table 3.
Fit Indices for the Latent Class Analysis of Diagnostic Groups

Models	Estimated parameters	BIC	Difference in BIC between models	Entropy	Group Sizes	Average posterior probabilities
1-class	6	785.162		1.00	112	
2-class	13	660.456	-124.71	.96	50, 62	1.00, 0.99
3-class	20	678.302	17.85	.96	25, 33, 54	0.99, 0.94, 0.99
4-class	27	699.935	21.63	.97	1, 25, 33, 53	1.00, 0.94, 1.00, 1.00
5-class	34	721.603	21.67	.93	1, 6, 25, 33, 47	0.93, 1.00, 1.00, 0.93, 1.00

Notes: BIC=Bayesian Information Criteria

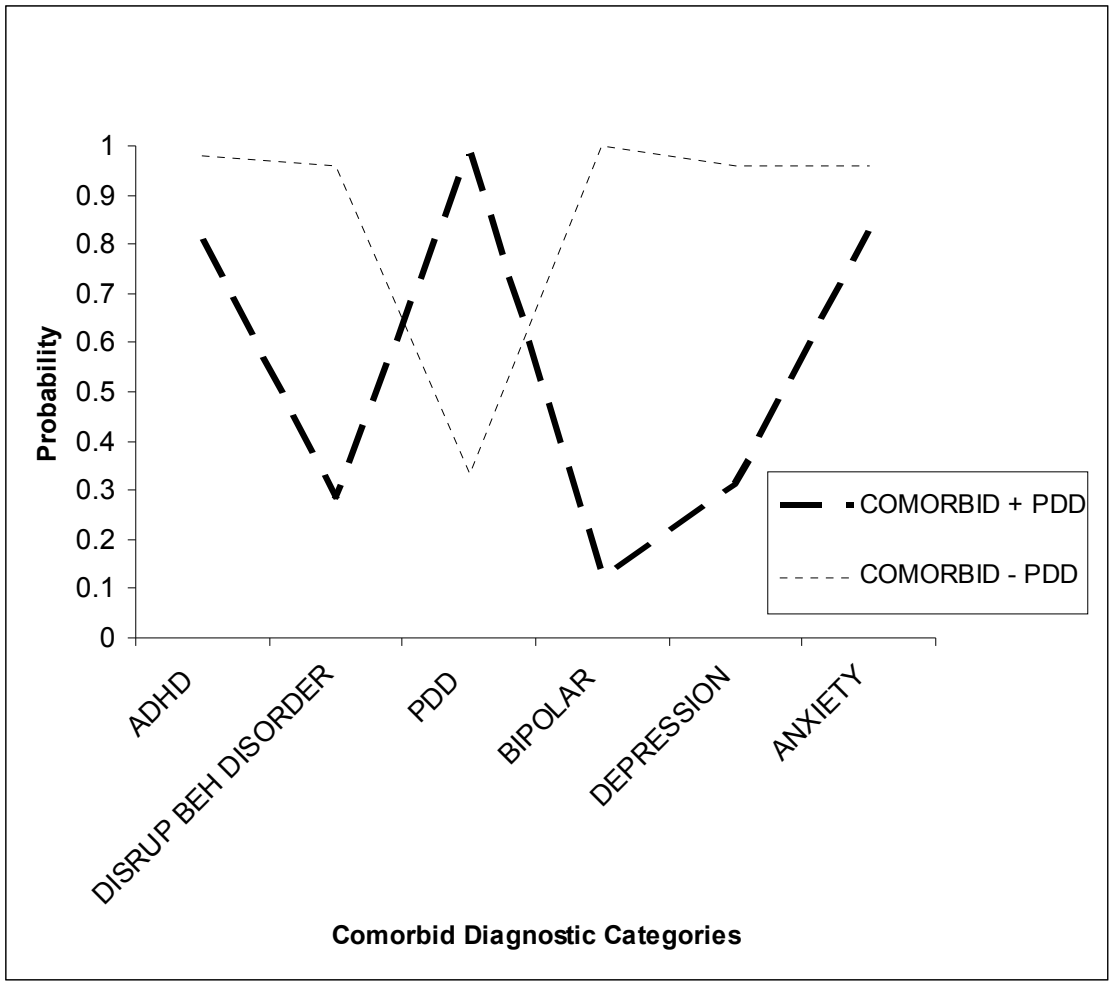

Figure 5. 2 class solution for Latent Class Analysis

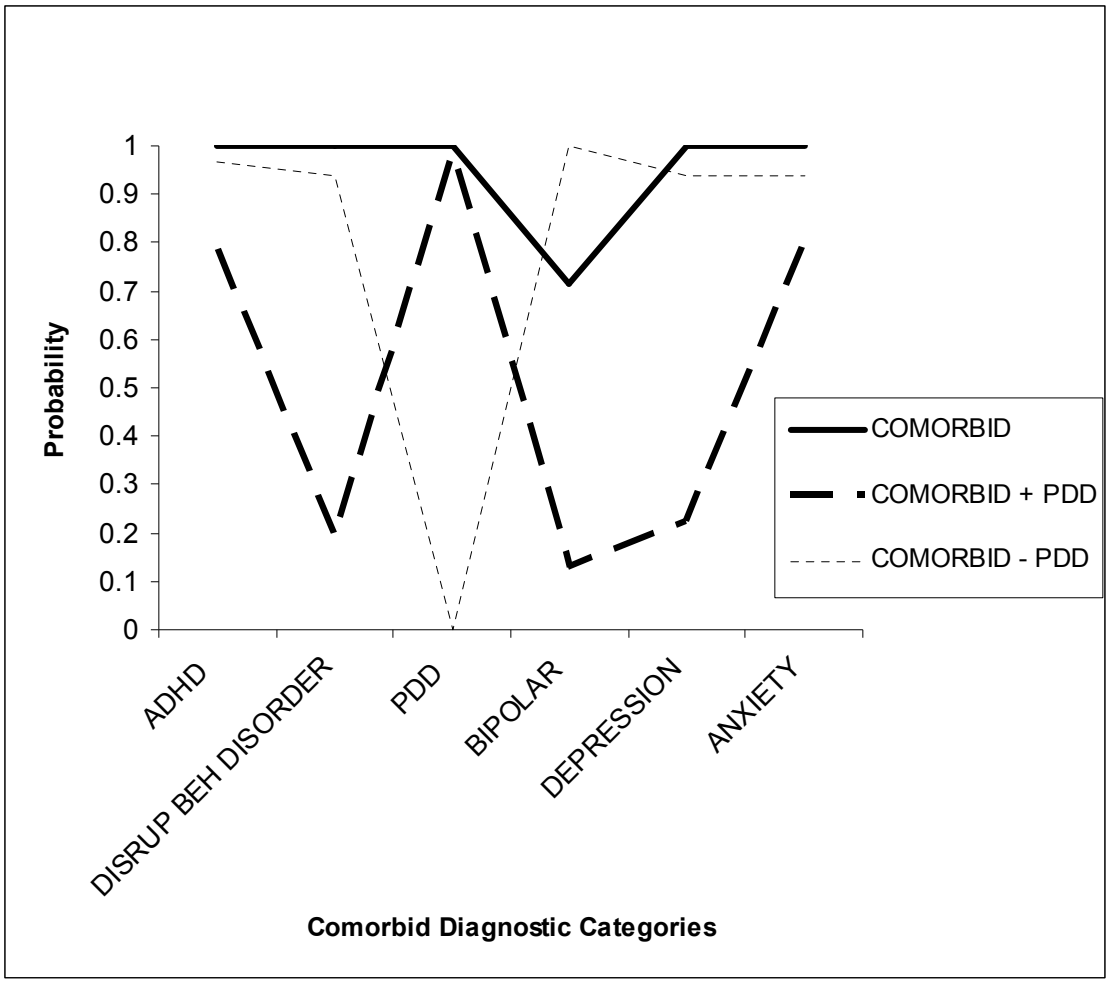

Figure 6. 3 Class Solution for Latent Class Analysis

Behavioral Profiles Reported by Parents

As expected, in the two-class solution, the children with a high probability of membership in either of the two latent classes demonstrated numerous differences in CBCL variables, as reported by their parents, compared to children in the Control group (Figure 7). The behavior profile for controls was fairly stable across all subscales, with all T-scores falling in the normative range of 46 - 53. Conversely, both of the latent classes displayed behavior profiles with elevated scores on problem behavior subscales and depressed scores on competence subscales. Specifically, children with a high probability of *Comorbid + PDD* class membership scored in the "clinically significant' range (T-score > 70), on Social Problems and Attention Problems subscales, and in the 'at risk' range (T-scores 67- 70) for Thought Problems subscale. This class scored significantly higher than the control group on all subscales ($p < 0.05$). Children with a high probability of *Comorbid - PDD* class membership scored in the 'clinically significant' range (T-score > 70), on the Anxious/Depressed, Aggressive Behavior, Attention Problems, and Social Problems subscales, and in the 'at risk' range (T-scores 67 - 70), on the Thought Problems subscale. This class scored significantly higher than the control group on all subscales, except the Activities competence subscale (Table 4.).

In addition, although the two latent classes displayed similar patterns of perceived behavior by parents, the children with a high probability of *Comorbid - PDD* class membership were rated by their parents as having significantly more problems on the Anxious/Depressed, Delinquent Behavior, and Aggressive Behavior subscales, and significantly less competence on the Social Competences subscale compared to children with a high probability of membership in *Comorbid + PDD* Class (Figure 7; Table 4.).

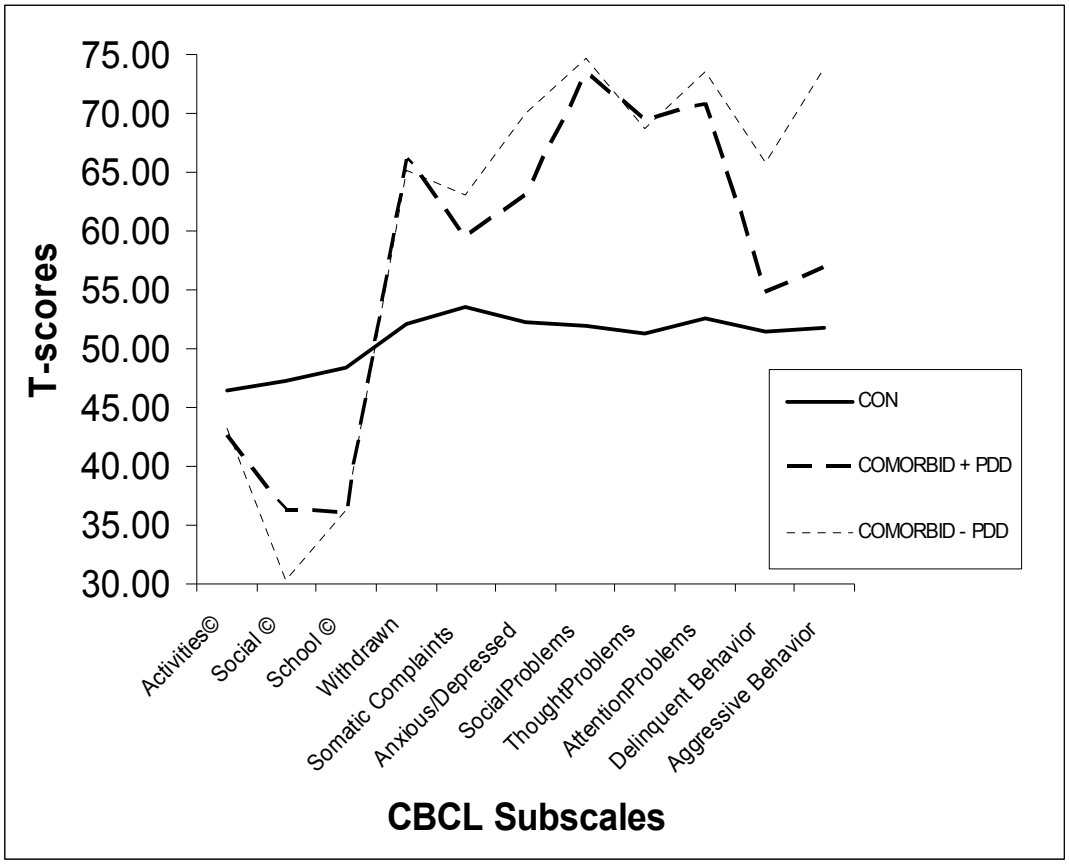

Figure 7. 2-class solution behavior profiles based on CBCL.

Notes. CON=Controls; ©=Parent Reported Competence Subscale; PDD=Pervasive Developmental Disorder

Table 4
Descriptive Statistics (Adjusted Mean [Controlling for Gender and Age] ± Standard Error) of CBCL-Parent Variables for 2 Class Solution Latent Class Classification

CBCL Subscales (T-scores)	*"Comorbid + PDD" Class*	*"Comorbid + PDD" Class n*	*"Comorbid - PDD" Class*	*"Comorbid - PDD" Class n*	*Controls*	*Controls n*	
Activities ©	42.50 ± 1.03	55	43.17 ± 1.89	41	46.57 ± 1.54	25	$F(4, 120) = 1.26$, *ns*
Social ©	36.14 ± 1.12 [b a]	52	30.31 ± 1.99 [b]	44	47.43 ± 1.62	25	$F(4, 120) = 18.26$, $p<.05$
School ©	36.05 ± 1.00 [b]	52	36.25 ± 1.10 [b]	42	48.50 ± 1.45	25	$F(4, 118) = 14.63$, $p<.05$
Withdrawn	65.99 ± 1.28[b]	56	65.34 ± 1.41[b]	45	52.01 ± 1.92	25	$F(4, 125) = 11.14$, $p<.05$
Somatic Complaints	59.39 ± 1.20[b]	56	63.08 ± 1.33[b]	45	53.71 ± 1.80	25	$F(4, 125) = 4.81$, $p<.05$
Anxious/Depressed	62.94 ± 1.28 [b a]	56	70.06 ± 1.42 [b]	45	52.31 ± 1.92	25	$F(4, 125) = 14.24$, $p<.05$
Social Problems	73.42 ± 1.23[b]	56	74.67 ± 1.37 [b]	45	51.69 ± 1.85	25	$F(4, 125) = 29.35$, $p<.05$
Thought Problems	69.65 ± 1.18[b]	56	68.59 ± 1.30[b]	45	51.36 ± 1.77	25	$F(4, 125) = 21.52$, $p<.05$
Attention Problems	71.08 ± 1.13[b]	56	73.55 ± 1.25 [b]	45	52.31 ± 1.70	25	$F(4, 125) = 28.43$, $p<.05$
Delinquent Behavior	54.96 ± .99 [b a]	56	65.78 ± 1.10 [b]	45	51.08 ± 1.49	25	$F(4, 125) = 20.69$, $p<.05$
Aggressive Behavior	57.06 ± 1.10 [b a]	56	73.79 ± 1.22 [b]	45	51.47 ± 1.66	25	$F(4, 125) = 38.90$, $p<.05$

Notes. CBCL = Achenbach Child Behavior Checklist
©=Parent Reported Competence Scale[a]= significantly different from *Comorbid – PDD* class; [b]=significantly different from CON

Thus, children with probable membership in the *Comorbid - PDD* Class had more behavioral deficits than those with probable membership in the *Comorbid + PDD* Class.

Behavior Profiles Reported by Teachers

As hypothesized, the children with a high probability of membership in the two diagnostic classes (*Comorbid + PDD* or *Comorbid – PDD*) demonstrated numerous differences in TRF variables compared to children in the Control group (Figure 8; Table 5). Similar to parent perceptions (CBCL) both latent classes displayed behavior profiles with elevated scores on problem behavior subscales and depressed scores on adaptive behavior subscales, whereas controls demonstrated stable scores on all subscales (range: 50-54). Children with a high probability of *Comorbid + PDD* Class membership scored in the 'at risk' range (T-score: 67-70) on the Thought Problems subscale. They also scored significantly higher than the control group on all clinical subscales except Delinquent Behavior and Somatic Problems subscales, and significantly lower than controls on all adaptive subscales except Working Hard (Table 5.). Children with a high probability of *Comorbid - PDD* Class membership did not score in the 'clinically significant' or 'at risk' range on any of the subscales. However, they scored significantly higher than the control group on almost all subscales (Table 5.).

Overall, controlling for age and gender, there was considerable similarity between the parent and teacher perceptions of behavior in the latent classes (Figures 7 & 8; Tables 4 & 5). Children with a high probability of *Comorbid - PDD* Class membership demonstrated significantly greater levels of Delinquency compared to children with a high probability of *Comorbid + PDD* Class membership (Figure 8; Table 5.). In addition although not statistically significant, teacher perceptions of Aggressive Behavior

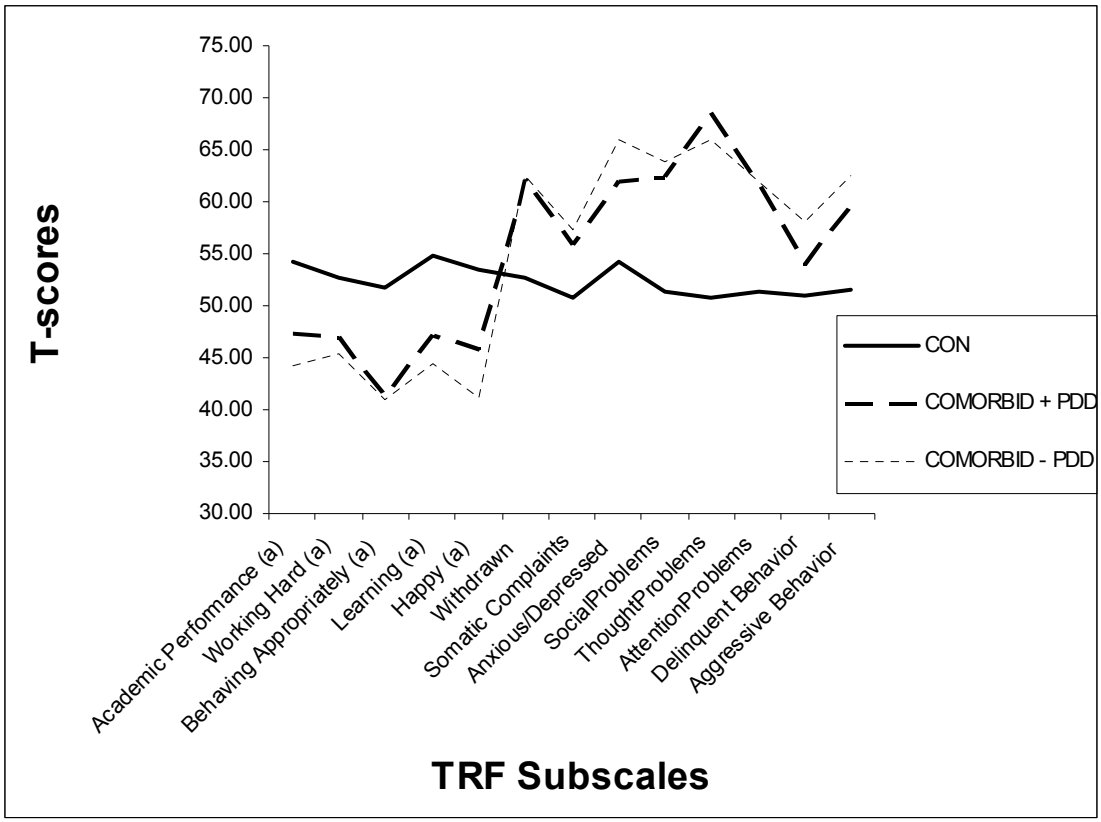

Figure 8. 2 class solution behavior profiles based on TRF.

Notes. CON=Controls; TRF= Teacher Report Form; (a) =Adaptive Functioning Subscale; PDD=Pervasive Developmental Disorder

Table 5
Descriptive Statistics (Adjusted Mean [Controlling for Gender and Age] ± Standard Error) of Outcome Variables for Latent Class Classification

TRF Subscales (T-scores)	*"Comorbid + PDD" Class*	*"Comorbid + PDD" Class n*	*"Comorbid – PDD" Class*	*"Comorbid – PDD" Class n*	*Controls*	*Controls n*	
Academic Performance (a)	46.99 ± 1.23 [b]	45	44.23 ± 1.40 [b]	34	55.74 ± 2.66	10	$F(4, 88) = 4.36$, $p < .05$
Working Hard (a)	47.00 ± 1.31	45	45.44 ± 1.53	33	52.67 ± 2.86	10	$F(4, 87) = 1.35$, *ns*
Behaving Appropriately (a)	41.29 ± 1.02 [b]	45	40.94 ± 1.17 [b]	34	50.99 ± 2.22	10	$F(4, 88) = 6.14$, $p < .05$
Learning (a)	46.99 ± 1.18 [b]	44	44.39 ± 1.36 [b]	33	55.54 ± 2.54	10	$F(4, 86) = 3.89$, $p < .05$
Happy (a)	45.74 ± 1.09 [b a]	43	41.26 ± 1.23 [b]	33	53.16 ± 2.33	10	$F(4, 85) = 6.71$, $p < .05$
Withdrawn	62.23 ± 1.30 [b]	46	62.53 ± 1.48 [b]	35	52.28 ± 2.86	10	$F(4, 90) = 2.89$, $p < .05$
Somatic Complaints	55.79 ± 1.15	46	57.32 ± 1.31	35	50.62 ± 2.53	10	$F(4, 90) = 1.47$, *ns*
Anxious/Depressed	62.07 ± 1.25 [b a]	46	65.98 ± 1.42 [b]	35	54.04 ± 2.74	10	$F(4, 90) = 4.20$, $p < .05$
Social Problems	62.43 ± 1.26 [b]	46	63.75 ± 1.44 [b]	35	50.79 ± 2.76	10	$F(4, 90) = 4.77$, $p < .05$
Thought Problems	68.27 ± 1.40 [b]	46	65.94 ± 1.59 [b]	35	51.99 ± 3.06	10	$F(4, 90) = 8.32$, $p < .05$
Attention Problems	61.71 ± 1.23 [b]	46	61.99 ± 1.40 [b]	35	50.45 ± 2.69	10	$F(4, 90) = 4.38$, $p < .05$
Delinquent Behavior	53.98 ± 0.86 [a]	46	58.10 ± .98 [b]	35	50.65 ± 1.88	10	$F(4, 90) = 4.36$, $p < .05$
Aggressive Behavior	59.47 ± 1.21 [b]	46	62.52 ± 1.37 [b]	35	51.99 ± 2.65	10	$F(4, 90) = 3.67$, $p < .05$

Notes. TRF = Achenbach Teacher Report Form; (a) = Adaptive Functioning [a]= significantly different from *Comorbid – PDD* class; [b]=significantly different from CON

demonstrated a trend in the same direction as the parent perceptions. Further, children with a high probability of *Comorbid - PDD* Class membership had significantly lower adaptive scores on the Happy subscale compared to *Comorbid + PDD* Class (Figure 8; Table 5.).

Overall, the 3-class solution yielded generally similar results on the behavioral profiles of the CBCL. A few differences between the 2- and 3-class solutions were that parents perceived children in the *Comorbid - PDD* Class to have higher scores on the Somatic Problems subscale than *Comorbid + PDD* Class in the 3-class solution, whereas they perceived children in the *Comorbid - PDD* Class to have lower scores on Social Competence, than those in *Comorbid + PDD* Class in the 2-class solution.

In the 3-class solution, the *Comorbid* Class (the class with the highest number of comorbid conditions and with the greatest likelihood of endorsing both BPD and PDD) also displayed significantly greater levels of parent-perceived Anxious/Depressed, Delinquent Behavior, Aggressive Behavior, and significantly lower levels of Social Competence compared to *Comorbid + PD*D Class. Taken together, the 2- and 3-Class solutions appear to paint similar pictures of parent perceptions.

The similarities between the 2- and 3-class solutions were less clear when looking at the TRF scores (see Table 5 and Figure 8). In both the 2- and 3-class solutions, children with a high probability of *Comorbid - PDD* Class (the class with the most number of children with a BPD diagnosis) membership were found to have significantly higher scores on the Delinquent Behavior scale, Anxious/Depressed scale, a trend toward significance on the Aggressive behavior scale, and significantly lower scores on the adaptive scale-Happy compared to children with a high probability of *Comorbid + PDD*

Class membership (the class with the most number of children with a ASD diagnosis). Similarly, in the 3 class solution, teachers perceived *Comorbid - PDD* Class to have lower scores on the adaptive scale-Working Hard, than those with a high probability of *Comorbid + PDD* Class membership, as well as significantly greater levels of Delinquent Behaviors in the *Comorbid* Class (the class with the highest number of comorbid conditions), compared to the *Comorbid + PDD* Class. This was also generally consistent with the TRF findings in the primary diagnostic groups as the BPD diagnostic group was perceived by teachers to have significantly greater levels of Delinquent Behaviors and Anxious/Depressed, and significantly lower scores on the adaptive Happy subscale compared to the ASD group (ASD, BPD, see Figures 1 & 2; Tables 1 & 2). Overall, parent perceptions were similar to teacher perceptions. Children in *Comorbid - PDD* Class in the 2 and 3 class models and the *Comorbid* Class in the 3-class model were rated as having more problems in the areas of Delinquent Behavior, Anxious/Depressed, Happy, Working Hard, and Academic Performance, at the level of trend or statistical significance.

Correlations between Parent and Teacher Perceptions

In order to better understand the relationship between the CBCL (parent) and TRF (teacher) variables, a Pearson product-moment correlation coefficient was computed for each pair of subscales (Table 6.). There was a moderate positive correlation between the CBCL and TRF subscales measuring anxiety/depression, thought problems, attention problems, aggression, delinquency, and social problems; the more modest correlation for somatic complaints did not achieve statistical significance (Table 6.).

Table 6
Pearson Product-Moment Correlations for CBCL and TRF

Subscale	*n*	*R*
Anxious/Depressed	91	0.52**
Thought Problems	91	0.44**
Attention Problems	91	0.39*
Aggressive Behavior	91	0.42**
Delinquent Behavior	91	0.59**
Social Problems	91	0.49**
Somatic Complaints	91	0.24

Note: *p<.001; **p<.0001

Brain Structure Volumes Assessed by Structural MRI

In order to examine differences in the temporal cortex, amygdala, and hippocampus volumes, volumetric data were compared between the latent classes. Figures 9 and 10 show volumes for the temporal cortex, the amygdala, and the hippocampus for the Control group and the latent Classes. There were no statistically significant mean differences in brain structure volume between the latent classes and controls on any of the neuroanatomical structures examined (Figure 9 and 10). However, given the small sample sizes and expected low levels of power, effect sizes (ES) were computed by dividing the mean difference between the groups by the pooled standard deviation. ES (*d*) of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (Cohen, 1988). There were small to moderate mean differences between the Control and *Comorbid + PDD* Class in the temporal cortex volumes (ES = .43), and the amygdala volumes (ES = .24). There were also small to moderate mean differences between the Control and the *Comorbid - PDD* Class in the temporal cortex volumes (ES = .20), amygdala volumes (ES = .35), and hippocampus volumes (ES = .39). Although these group differences were statistically non-significant, the observed mean differences in the neuroanatomical structures across the latent classes that were in the range of small effect sizes suggest that future studies should assess these structures in larger samples or in samples that are more diagnostically homogeneous**.**

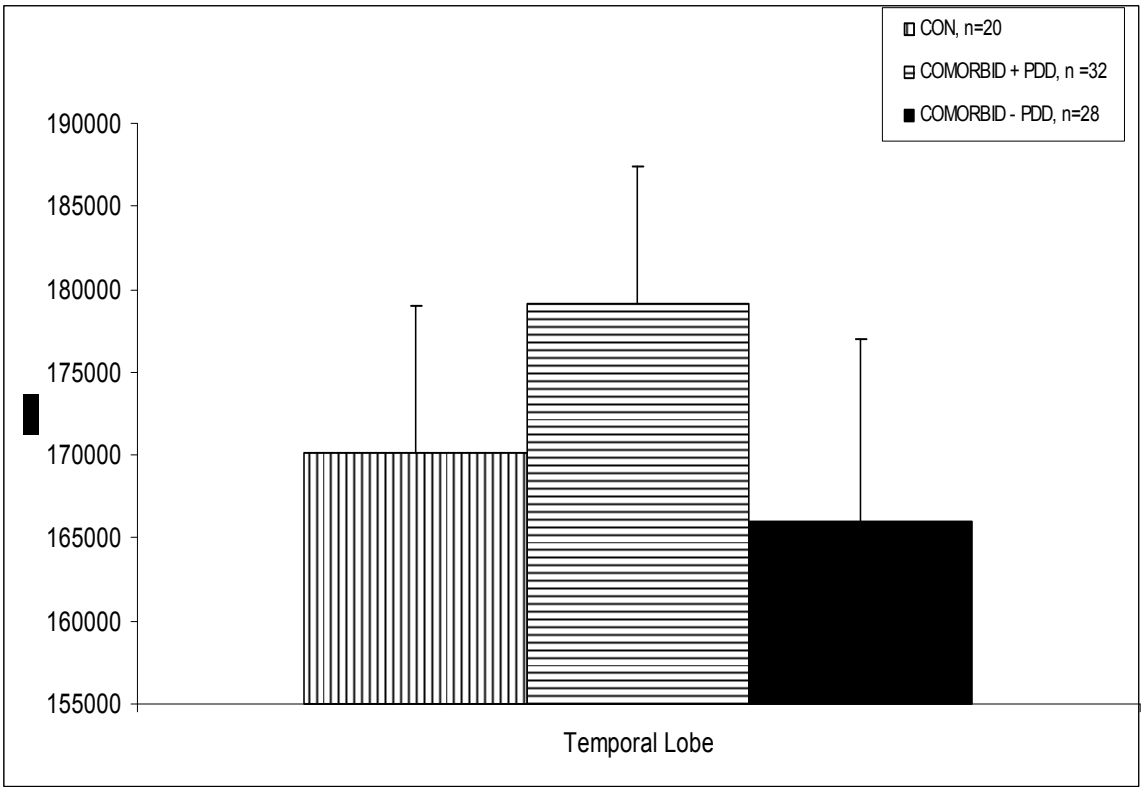

Figure 9. Volumes of temporal cortex by latent class.

Notes. CON=Controls; PDD=Pervasive Developmental Disorder

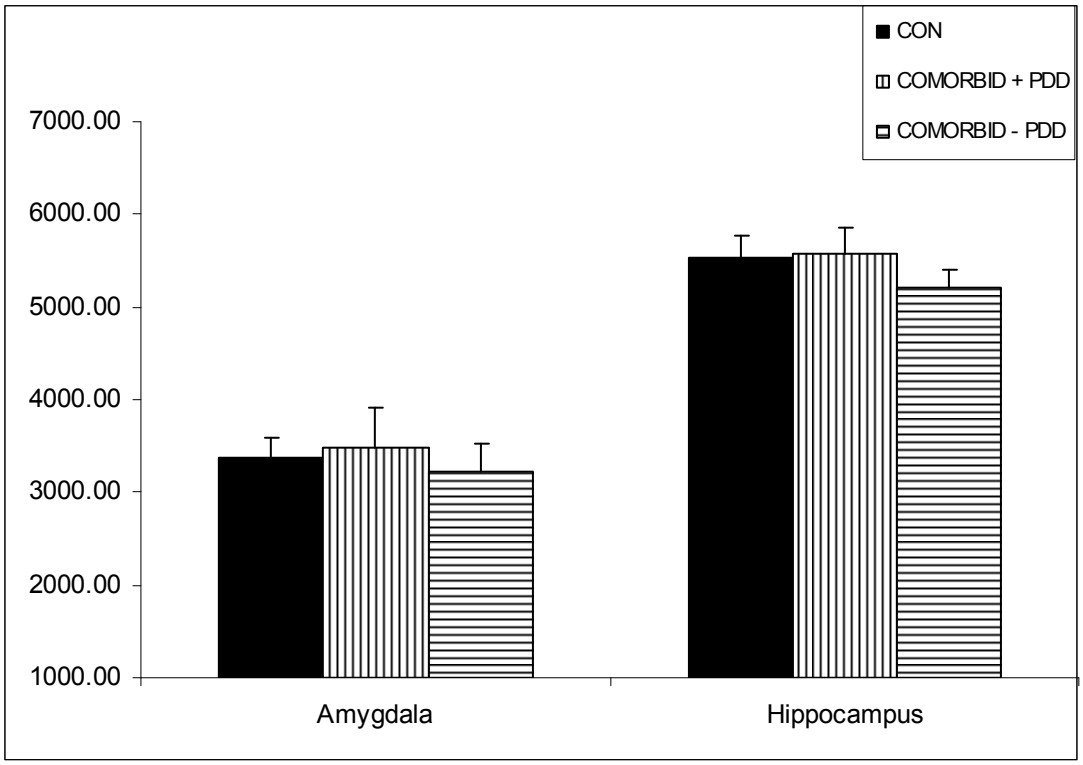

Figure 10. Volumes of amygdala and hippocampus by latent classes.

Notes. CON=Controls (Amygdala, n=11; Hippocampus, n=11); COMORBID + PDD=Comorbid plus Pervasive Developmental Disorder (Amygdala, n=18; Hippocampus, n=17); COMORBID - PDD=Comorbid minus Pervasive Developmental Disorder (Amygdala, n=18; Hippocampus, n=16)

Variability in Diagnostic Groups and Latent Classes

Recall that the latent class analysis approach was used to explore whether heterogeneity in problem behaviors and brain structure volumes within standard diagnostic classification groups could be reduced, and thus between group differences amplified by identifying unobserved classes based on six common psychiatric diagnostic categories in childhood. To further probe this idea, the standard deviations of CBCL behavioral reports and brain structure volumes of the BPD diagnostic group and the latent class containing the most individuals diagnosed with BPD (*Comorbid - PDD* Class) were qualitatively compared. Similarly, the standard deviations of the ASD diagnostic group and the latent class containing the most individuals diagnosed with ASD *(Comorbid + PDD* Class) were qualitatively compared. Overall, the variability in the diagnostic groups was indistinguishable from that in the associated two latent classes for the CBCL subscales (Figures 11 & 12), the TRF subscales (Figures 13 & 14), and the MRI structures (Figure 15). Thus, although the behavioral and neuroanatomical profiles of the two latent classes were different from the control group, profiles within the clinical groups were not more homogeneous when utilizing the 2-class latent model. This suggests that the latent classes did not provide an improvement in reducing heterogeneity of diagnostic classification, compared to standard DSM-IV criteria in terms of behavior problems and competencies and structural neuroanatomical features.

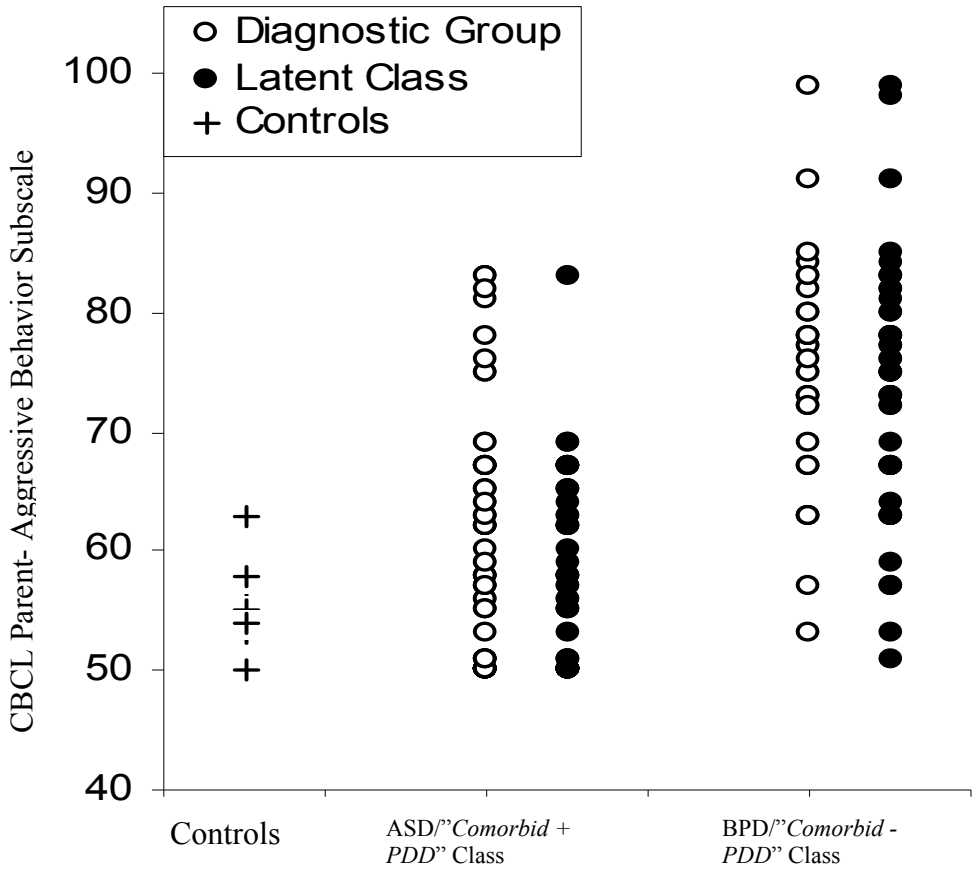

Figure 11. Scatterplot of aggressive behavior subscale for CBCL.

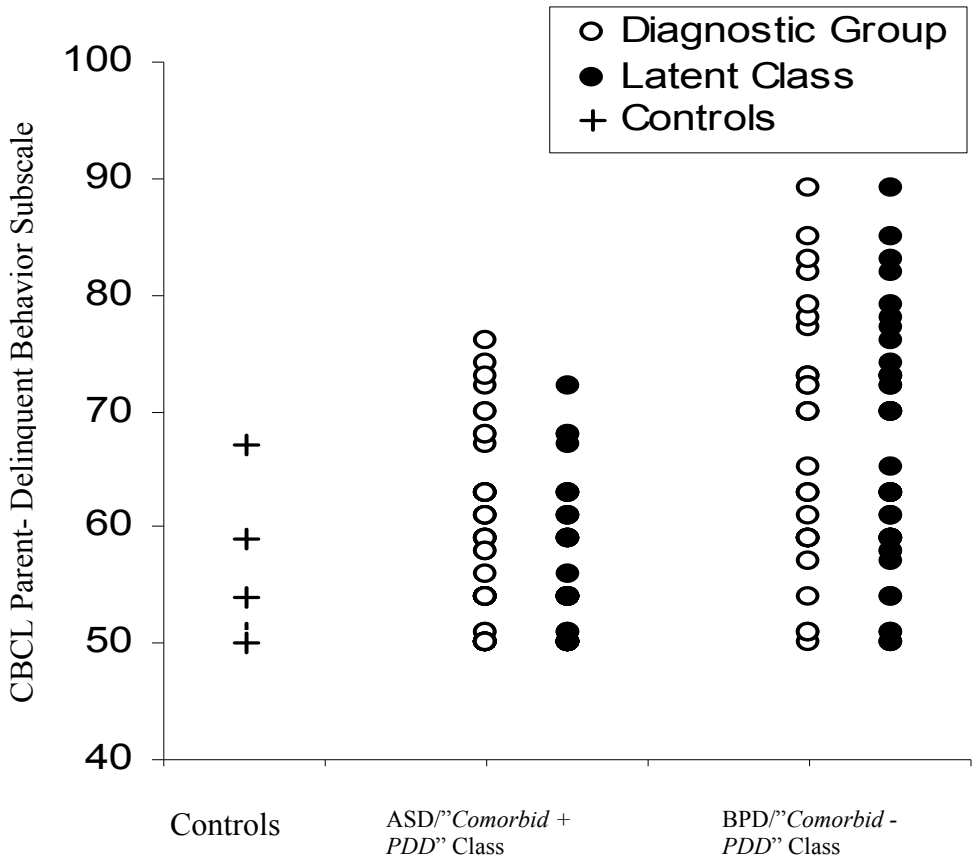

Figure 12. Scatterplot of delinquent behavior subscale for CBCL.

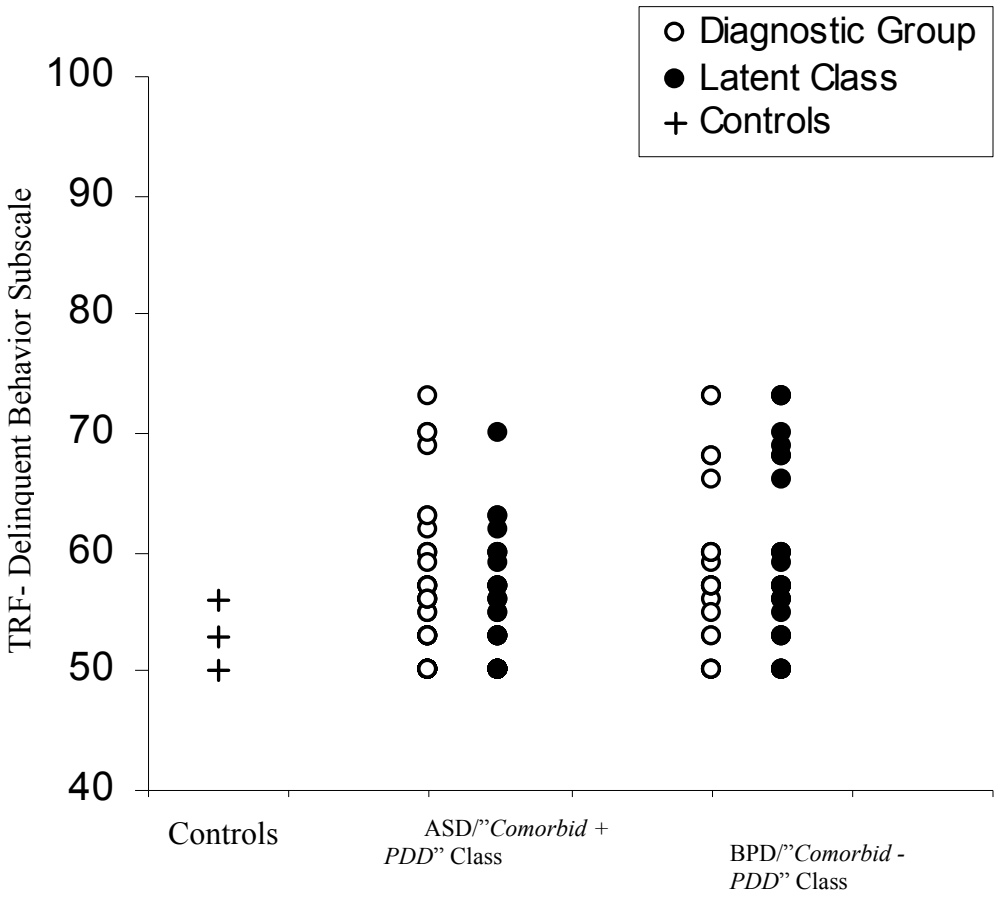

Figure 13. Scatterplot of TRF delinquent behavior subscale.

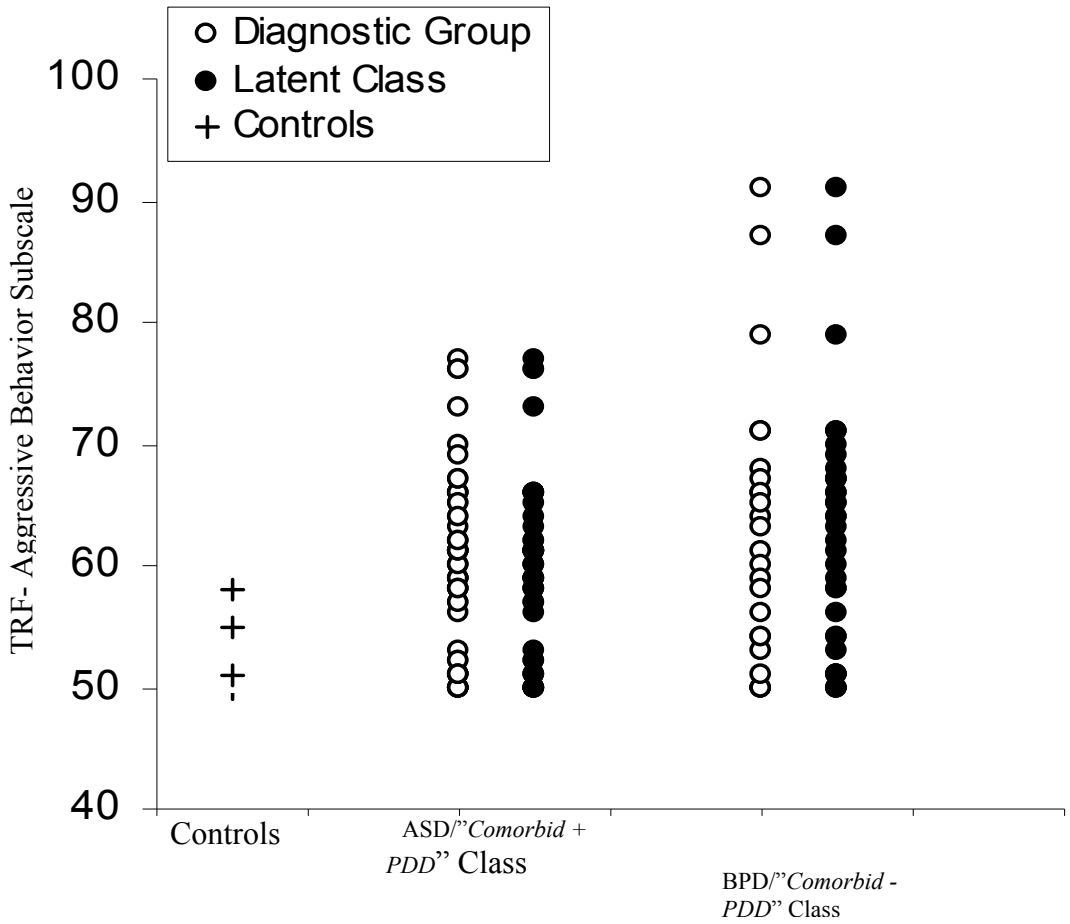

Figure 14. Scatterplot TRF aggressive behavior subscale.

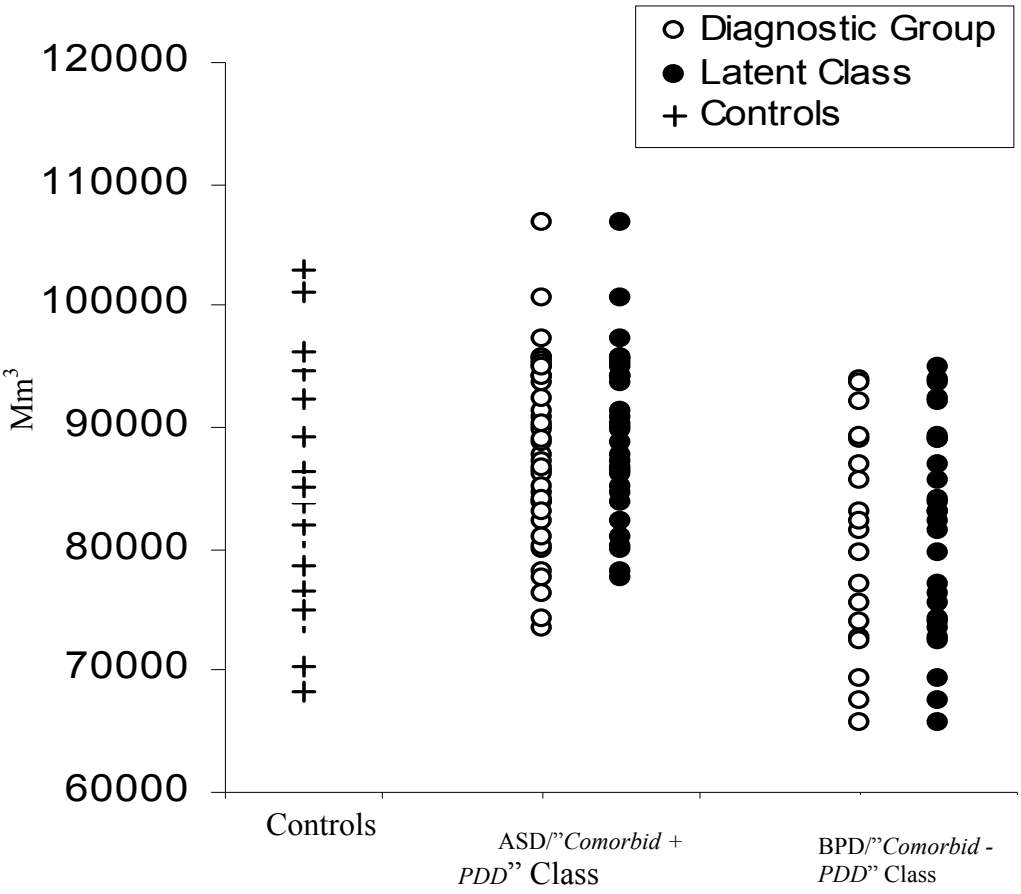

Figure 15. Scatterplot left temporal cortex volume.

CBCL Profiles of Children with BPD

Biederman et al. (1995) defined a CBCL behavioral profile on the basis of clinically significant elevations (T-scores > 70) on the Attention Problems, Aggressive Behavior, and Anxious/Depressed syndrome subscales in search of a tool to distinguish children with BPD from children with other psychopathologies. In our sample, 55% of children who were clinically diagnosed with BPD met criteria on this behavioral profile. In terms of the latent classes, 9% of *Comorbid + PD*D Class and 56% of *Comorbid - PDD* Class met criteria on this behavioral profile. Thus, in the present sample, Biederman's behavioral profile did not closely coincide with either a primary BPD diagnosis or either latent class. Further, those children with a primary BPD diagnosis who also met criteria for the Biederman's behavioral profile did not seem to differ from those who did not meet criteria in any brain structure studied.

CHAPTER IV

Discussion

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) is the primary source for diagnostic information in the United States. As research and clinical science have progressed, the DSM has evolved, often shifting diagnostic criteria, renaming disorders, or clarifying distinctions between disorders through more specifically defining diagnostic criteria. However, due to its use of a categorical classification system, there remains substantial heterogeneity within a given diagnosis as well as overlapping symptoms between diagnoses (American Psychiatric Association, 2000). This raises substantial obstacles for clinicians on the front line who often struggle with assigning appropriate diagnoses and for researchers who work to understand the etiology of, and develop treatments for, these disorders.

Proper diagnosis of psychological disorders in children and young adults is especially important because a psychological diagnosis can have major lifetime ramifications and substantially influence treatment approach. Two major childhood disorders that continue to be challenging to diagnose and treat are bipolar disorder (BPD) and autistic disorder. BPD has traditionally been thought of as a disorder of adolescence and adulthood, and the controversy surrounding a diagnosis of pediatric BPD continues. In fact, the inclusive criteria for BPD frequently overlap considerably with other comorbid disorders, such as ADHD (Wozniak, et al., 1995), anxiety disorders (Dickstein,

et al., 2005), and substance use disorders (Wilens, 1999). Furthermore, the inclusion of 'irritable and elevated/expansive mood' as a DSM-IV-TR criterion of BPD in children, but not adults, as well as the increasing rates of BPD in youth (Blader & Carlson, 2007) has added to the disagreement among clinicians over the presentation of BPD in children.

Similarly, difficulties in accurately diagnosing an autistic disorder stem from the extensive heterogeneity in the presentation of the disorder. Moreover, the prevalence of the autism spectrum disorders (ASD), a term that has been developed to encompass 'the spectrum,' (National Institute of Mental Health) has increased dramatically over the last 30 years, raising questions about the reliability of the diagnostic categories. It is now more common to diagnose developmental disorders on the 'autism spectrum'(National Institute of Mental Health). This spectrum includes autistic disorder, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified. Compounding diagnostic problems is the finding that ASD often co-occurs with social anxiety disorder, Attention Deficit Hyperactivity Disorder (ADHD), and Oppositional Defiant Disorder (ODD) (American Psychiatric Association, 2000).

The controversies surrounding these two disorders (i.e., BPD and ASD) demonstrate the limitations of using a categorical classification system that is based exclusively on clinically observable or reported psychological symptoms. One potential method of bolstering clinicians' ability to identify and differentiate psychiatric disorders is to consider information other than reported or observable symptoms. For example, identification of the neuroanatomical correlates of psychiatric disorders may assist in streamlining the diagnostic process. Another strategy that has been explored to further clarify diagnostic categories is developing behavioral profiles that go beyond the DSM

criteria (Biederman, et al., 1995). These strategies would enhance differential diagnosis by capturing a more complete understanding of the psychological and biological processes that underlie childhood psychopathology.

The utility of neuroanatomical and behavioral data in informing diagnosis, however, has been limited by inconsistencies in the literature. The presence of comorbidity makes it difficult to accurately capture the distinctive neuroanatomical and behavioral features of a given diagnosis (Matson & Nebel-Schwalm, 2006). This dissertation aimed to utilize comorbid diagnostic information to better characterize children with a primary diagnosis of ASD or BPD, and to identify clearer distinctions in terms of behavior and structural neuroanatomical features of the temporal cortex due to its role in mood regulation and emotional memory (Martin, 2003).

The Latent Class Analysis (LCA) Approach

Latent class analysis (LCA) can be a valuable analytic tool for research as it explores complex interactions among variables to more realistically characterize the way that individuals function and develop (Bates, 2000; Magnusson, 1998). LCA identifies homogeneous classes of individuals who are similar to those within a class, yet sufficiently different from those in other classes. This empirical, data-oriented process parallels the evolving goal of the DSM to appropriately classify individuals as they are better understood over time, essentially teasing apart diagnoses in order to classify individuals in a manner that best communicates the nature of their underlying psychopathology.

In this dissertation, LCA was proposed as a potentially useful analytic strategy to help tease apart the complex patterns of comorbidity and its effects on behavioral profiles

and neuroanatomical features. The results, however, did not support the utility of LCA in this particular application. The derived latent classes were neither more homogeneous than the DSM-IV based diagnostic groups, nor did these classes clarify the role of behavior and temporal cortex structures in childhood psychopathology. Indeed, the two latent classes formed with the best-fit model were composed of mostly the same individuals that made up the original diagnostic classes.

Because the primary goal of this dissertation was to characterize the role of comorbid conditions in order to better understand the diagnostic classes themselves, as well as their role in relation to behavior profiles and neuroanatomical correlates, a 3-class solution was also considered. In this model, the individuals with ASD, who also demonstrated four or more comorbid diagnostic conditions, shifted into a distinctively high comorbid class. However, high levels of comorbidity remained in both other latent classes nonetheless. Thus, the latent models (nor the diagnoses) were unable to categorize individuals solely based on levels of comorbidity or patterns of overlapping symptomology. Moreover, as with the 2-class solution, the 3-class solution, did not decrease within-group heterogeneity in terms of behavior profile or neuroanatomical correlates.

Although the results did not support the use of the LCA, a number of alternative explanations should be considered. Specifically, one alternative explanation may be that although these results may seem to lend support to the presence of convergent validity for the diagnostic classes, this may be due to the use of diagnostic-level data in the LCA rather than symptom-level data. In addition, these findings are consistent with a breadth of research that has been unable to demonstrate “natural boundaries between related

symptoms" (Dalal & Sivakumar, 2009, pg. 313). Thus, other potential explanations could be that this inability to tease apart the heterogeneity that exists among psychiatric disorders is due to: (1) "Psychopathology does not consist of discrete disease entities," (2) "Psychopathology does consist of discrete disease entities, but these entities are not reflected by current diagnostic categories," or (3) "The nature of psychopathology is intrinsically heterogeneous, consisting in part of true disease entities and in part of reaction types and maladaptive response patterns" (Dalal & Sivakumar, 2009, pg. 314). In this dissertation, the LCA utilized comorbid diagnostic information in the analysis to create more homogeneous categories. However, simply using the comorbid diagnostic categories did not decrease heterogeneity of behavioral profiles or anatomical abnormalities in volume.

Other researchers have attempted to explain the concept of comorbidity in a different way, by describing a set of comorbidity models (Klein & Riso, 1993; Neale & Kendler, 1995). For example, the Multiformity model explains heterogeneity in the form of a liability, or "the possibility that multiple pathways from same liability lead to different manifestations of that liability"(Krueger & Markon, 2006, pg. 6). This model assumes that two (A & B) theoretical liability factors are uncorrelated, but that both factors can cause symptoms of two different disorders. Thus, "an individual who is elevated on one liability factor might meet criteria for two disorders [Comorbid], because a single liability can be expressed through multiple disorders" (Krueger & Markon, 2006, p. 7). Perhaps the present study did not create more homogeneous groups or identify differences in neuroanatomy and behavior profiles because it is not the disorders themselves that should be considered, but instead a latent liability, or indirectly observed

propensity to develop directly observed or manifest disorders (Krueger & Markon, 2006). Unfortunately, identifying these underlying liabilities remains a challenge.

Behavioral Profiles

It was predicted that the heterogeneity would be observed in the behavioral profiles of children within the diagnostic groups of ASD or BPD, and that the behavioral profiles within each latent class would be more homogeneous. However, results did not support this hypothesis as behavior profiles were not more homogeneous when utilizing the classes derived from the LCA.

Although the hypotheses of this study were not supported, there are some important clinical implications for the results. Not only were the behavioral profiles of the diagnostic groups and their associated latent classes indistinguishable in terms of within-group variability, behavioral outcomes from the CBCL and TRF revealed numerous specific similarities between diagnostic groups and their associated latent classes. Specifically, parents perceived children with an ASD diagnosis to have clinically significant levels of Social Problems, Thought Problems, and Attention Problems. Similarly, parents perceived children with a high probability of *Comorbid + PDD* Class membership (the class with the highest number of children diagnosed with ASD) to have clinically significant levels of Social and Attention Problems, and to be 'at risk' for Thought Problems and being Withdrawn. Clinically significant elevation on the Thought Problems subscale supports previous research that found the Thought Problems subscale to distinguish healthy children from children diagnosed with autism (Rescorla, 1988).

A similar pattern of results was found for children diagnosed with BPD and their associated latent class. Specifically, parents perceived children with a BPD diagnosis to

have clinically significant levels of Anxious/Depressed, Attention Problems, Aggressive Behavior, and Social Problems. The same subscales were in the clinically significant range for children with a high probability of belonging to the *Comorbid – PDD* class. In addition, the *Comorbid – PDD* class also was perceived by parents to be in the 'at risk' range for the Thought Problems subscale. Although these results indicate that the use of LCA did not reveal a different or distinguishable profile of behavior which might have given evidence for more directly considering comorbidity in the diagnostic process, elevated scores on the Anxious/Depressed, Attention Problems, Aggressive Behavior, subscales for both the BPD group and the *Comorbid – PDD* class do support Biederman et al.'s (1995) behavior profile. As a result, clinicians who initially receive CBCL profiles of behavior that include clinically significant level of the Anxious/Depressed, Attention Problems, Aggressive Behavior, subscales, may consider exploring symptomology consistent with a diagnosis of BPD, and consider the possibility of co-occurring psychopathology.

Another noteworthy pattern of results was that although there was a correlation between the CBCL and TRF on many of the subscales, teachers consistently perceived behavior to be less problematic than parents. Teachers frequently reported scores in the 'at-risk' range whereas parents were more likely to report scores in the 'clinically significant' range. For example, parents tended to rate the clinical groups (both when considering DSM-IV-based primary diagnostic grouping as well as the latent classes) as having worse adaptive skills and worse behavior problems than teachers.

Clinically, these results deflect attention away from the issue of diagnostic groups, and toward the varying perceptions of teachers and parents. The differences in

perception of behavior between parents and teachers have been well supported, particularly with regard to internalizing symptoms (Glaser, Kronsnoble, & Warner - Forkner, 1997; Rosenberg, 1988). The demands of a classroom environment are often more demanding and different from those at home. Rules and expectations are often clearly defined in a school setting and there is usually less unstructured time than there is at home. Peers in the classroom as well as higher demands are often influential in the school setting. Thus, student behavior may often be legitimately different in school compared to home. Nonetheless, rater effects such as leniency and halo effects must also be considered (Thorndike, 1920). Although these reasons may be contributing factors to the teachers' perceptions, the reasons for this discrepancy between parent and teacher report cannot be determined by the present study.

Neuroanatomy

Prior studies comparing the volume of the temporal cortex, amygdala, and hippocampus in healthy children to those diagnosed with an ASD or BPD have been inconsistent (D.P. Dickstein, et al., 2005) (Frazier, et al., 2005). The present study hypothesized that the discrepancies between studies were at least partially due to within-group heterogeneity and the influence of comorbid conditions on an individual's neuroanatomical profile. Accordingly, it was predicted that because latent classes would consist of a more homogeneous group of children, the subtle neuroanatomical differences associated with childhood psychopathological conditions would be more readily detectable. This, however, was not supported. The volumes of the temporal cortex, amygdala, and hippocampus were equally heterogeneous in the latent classes as in the empirically derived DSM-IV-based diagnostic categories. Further, the structural volumes

of the control group did not statistically differ from either diagnostic group or either latent class. However, due to the small group sizes and limitations in power, effect size (ES) measurements were also computed. Small and medium effect size differences were found between the control group and the ASD group as well as the control group and the BPD group in the examined structures, possibly suggesting subtle effects that may require larger samples, or perhaps more importantly, an approach that identifies more homogeneous classes. Similar effect sizes were also found between the latent classes and controls. Although volume differences do not seem to aid in differential diagnosis, they may have an important role in understanding neurocognitive weaknesses and thus, may contribute to the development of treatment and perhaps educational planning.

The lack of differentiation among disorders may also have an impact on identifying the differences in neuroanatomical structures. Specifically, diagnoses of individual symptoms that make up aspects of disorders may have independent, possibly competing effects on brain structures, or the brain structures might have independent or competing effects on symptoms or a constellation of symptoms. Thus, the quest to identify a particular brain structure related to a psychiatric disorder continues to be a challenge. Furthermore, because the LCA performed in this study did not seem to be able to differentiate groups based on comorbidity patterns, it makes sense that the lack of differentiation between classes was fairly consistent with the lack of differentiation between diagnostic groups.

Limitations

This study involved some important limitations worth noting. First, it is possible that a larger sample would have helped to identify statistically significant differences in neuroanatomical structures between diagnostic groups and/or latent classes. Moreover, using diagnostic information in the LCA may not have fully captured the comorbidity present in the sample. For example, more homogeneous classes may have been identified if symptom level data were used in the LCA instead of diagnostic categories, as using diagnostic categories does not account for the individual's unique constellation of symptoms.

Another area of limitation may include the use structural MRI data. This study examined the relationship between diagnosis/class and neuroanatomy via MRI data, a purely volumetric measurement. The use of structural MRI data only captures the volume of the neuroanatomical structures under study; it does not investigate the role of the neural networks or functional activation in the temporal cortex structures during performance of cognitive or other tasks that might play a key role in these disorders. As technology and science has advanced, new techniques for analyzing the neurological basis of psychiatric disorders have been developed. Specifically, technology such as Functional Magnetic Resonance Imaging (fMRI), which goes beyond the traditional MRI technology of measuring volumes of brain structures, and is able to measure brain activity through the hemodynamic response, or change in blood flow, related to neural activity in different areas of the brain. Future research on psychiatric disorders and their relationship to the neurological system should utilize both structural and functional

neuroimaging methods to further develop our understanding of the neurobiological basis of psychiatric disorders such as ASD and BPD.

Moreover, future research should also consider exploring the role of other brain structures and networks beyond the temporal cortex. For instance, research has also implicated the frontal lobes and the cerebellum in Autism (Amaral, Schumann, & Nordahl, 2008), and the globus pallidus, caudate, putamen, and thalamus in BPD, (DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004), but were outside the scope of this dissertation.

Conclusions

Although the results of this study do not support the role of comorbidity in identifying more homogeneous groups of individuals with psychiatric disorders, researchers and clinicians continuously face the task of how to improve differential diagnoses so that communication among clinicians and researchers is consistent and uniform and clinicians can best plan for treatment. The field recognizes the importance and utility of a valid classification system as the American Psychiatric Association has been working on the newest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), which is projected for completion in 2013. The task force working on developing the DSM-V has publicized a few major areas of proposed revisions, one being the inclusion of an official diagnostic category of 'autism spectrum disorders' which would include autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder (not otherwise specified). The DSM-V is also proposed to include a dimensional component that would provide clinicians with a way to include 'cross cutting' symptoms that exist across a number of different

diagnoses, as well as evaluate the severity of symptoms ("APA Announces Draft Diagnostic Criteria for DSM-5, New proposed changes posted for leading manual of mental disorders," 2010). This would be a significant change from the purely categorical classification system of the DSM-IV and in theory may help better characterize symptomology that do not fit neatly into one diagnosis.

At present, many researchers are not able to consider etiological information for classification due to the lack of understanding in this area. Researchers are left to consider individuals and/or groups of people with little in common except a DSM diagnosis of a Pervasive Developmental Disorder or Bipolar disorder. As a result, discerning among the three proposed hypotheses by Dalal & Sivakumar (2009) is a significant challenge. For example, if researchers are not yet able to demonstrate that psychopathology can be distinguished into discrete disease entities, then the other theories that state that "Psychopathology does consist of discrete disease entities, but these entities are not reflected by current diagnostic categories," and "The nature of psychopathology is intrinsically heterogeneous, consisting in part of true disease entities and in part of reaction types and maladaptive response patterns," (Dalal & Sivakumar, 2009, pg. 314) are unable to be tested.

Diagnoses and comorbid diagnoses, based on only observable symptomology, and not etiology, has impeded the search for understanding the cause of psychiatric disorders and in turn their appropriate classification. For instance, perhaps, as hypothesized, it is the lack of homogeneity within diagnostic groups that limits researchers' ability to identify distinct underlying mechanisms which differentiate disorders, but, additional information, not just comorbid diagnoses based on the current classification system, is

needed in order to create these homogeneous groups. Over time, with advances in technology, the fields of molecular genetics and neuroscience will continue their efforts to identify additional information about the genetic and neurological basis of these psychiatric conditions. However, the use of this knowledge to influence psychiatric classification will continue to be impacted by cultural, social and economic forces that have an effect on the population's perception of psychiatric disorders and the field of psychiatry in general.

Researchers continue to diligently conduct research on the genetic and neurological underpinnings that may underlie a number of diagnoses. Specifically, there is growing evidence that disorders that are classified under the same larger title (i.e. Anxiety Disorders) do not all seem to rely on the same neural networks (Dalal & Sivakumar, 2009). As a result, future versions of the DSM may benefit from focus on creating a classification system with two major axes: One etiological, using neurobiological and genetic organizing concepts, and the other using syndromal and/or behavioral-dimensional (similar to the current system) (Dalal & Sivakumar, 2009) in order to allow researchers the opportunity to link etiology to diagnosis and symptom presentation while keeping the current classification system to continue communication in the field as etiology is being further explored (Jablensky & Kendell, 2002). As advances in medicine and technology increase, the clarification of the genetic and neurological underpinnings of psychiatric disorders will undoubtedly lead to a better understanding of the nature of psychopathology.

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APPENDIX A

Asperger's Disorder: Diagnostic Checklist

____ A. Qualitative impairment in social interaction, as manifested by at least two of the following:

____ 1. Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction.

_____

_____

_____

____ 2. Failure to develop peer relationships appropriate to developmental level.

_____

_____

_____

____ 3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people).

_____

_____

_____

____ 4. Lack of social or emotional reciprocity.

_____

_____

_____

____ B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

____ 1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus.

_____

_____

_____

____ 2. Apparent inflexible adherence to specific, nonfunctional routines or rituals.

_____

_____

_____

____ 3. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements).

_____

_____

_____

____ 4. Persistent preoccupation with parts of objects.

_____

_____

_____

____ C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

_____

_____

_____

____ D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases by age 3 years). Describe language development.

_____

_____

_____

____ E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood. Describe cognitive development.

_____

_____

_____

____ F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

_____

_____

_____

Language Pragmatics:

_____

_____

_____

Description of Relatedness to Others:

_____

_____

_____

HFA Supplement:

____ A2. Qualitative impairments in communication as manifested by at least one of the following:

____ a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

_____

_____

_____

____ b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

_____

_____

_____

____ c. stereotyped and repetitive use of language or idiosyncratic language

_____

_____

_____

____ d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

_____

_____

____ B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

_____

_____

_____

____ C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

_____

_____

_____