BEHAVIOURAL PROFILES WITHIN AND ACROSS ASD, ADHD, AND OCD

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TITLE:	Internalizing and Externalizing Problems in Children with ASD, ADHD, and OCD: Identifying Behavioural Profiles Within and Across Diagnostic Categories
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Lay Abstract

ASD, ADHD, and OCD are heterogenous neurodevelopmental disorders (NDDs) with some overlapping clinical characteristics and etiological factors. Internalizing and externalizing behavioural problems persist across these three NDDs, and in this study, are used to identify unique behavioural profiles. Study findings reveal four groups with distinct behavioural profiles of internalizing and externalizing problems that are not identified by the original diagnostic groups. This empirical way of classifying children with similar behavioural profiles can be used in combination with diagnostic labels to enhance transdiagnostic interventions that can be tailored to each child's needs.

Abstract

Background: Emerging evidence suggests that there is both within-disorder heterogeneity and across-disorder overlap in the clinical presentation of children with ASD, ADHD, and OCD. Two prevalent dimensional phenotypes in children with these NDDs that warrant close attention, and are suitable for cross-disorder investigation, are internalizing and externalizing problems.

Objectives: The current study uses a data-driven, diagnosis-agnostic approach to identify homogenous clusters that describe behavioural profiles of internalizing and externalizing problems within and across ASD, ADHD, and OCD.

Methods: Data on 1565 children (M = 10.76 years) were drawn from the Province of Ontario Neurodevelopmental Disorder (POND) Network. Non-hierarchical clustering approaches were used to empirically derive, distinct behavioural profiles of internalizing and externalizing problems indexed by the Child Behavior Checklist (CBCL). Empirically derived groups were characterized using measures of adaptive functioning indexed by the Adaptive Behaviour Assessment (ABAS-II), and interpreted in relation to original diagnoses.

Results: Cluster analyses identified four distinct behavioural profiles that cut across all diagnostic groups: High Internalizing Externalizing (HIE; 15%), High Externalizing (HE; 21%), Low Internalizing Externalizing (LIE; 38%), and Low Externalizing (LE; 26%). Derived clusters had variable levels of adaptive behaviours and reflected different behavioural profiles than the ones defined by the original diagnostic category groups of ASD, ADHD, and OCD.

Conclusion: Data-driven, diagnosis-agnostic approaches can inform our understanding of the between and within phenotypic heterogeneity seen in ASD, ADHD, and OCD. Empirical ways of classifying children with homogeneous behavioural profiles may complement existing diagnostic models in our efforts to develop cross-disorder, more personalized interventions for children with neurodevelopmental disorders.

Keywords: internalizing behaviours, externalizing behaviours, behavioural phenotypes

In loving memory of my Teta,

Raqia Ata Tayeh Assi

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I would like to extend my sincerest gratitude to my supervisor, Dr. Stelios Georgiades, for the opportunity to grow under your guidance. I value all I have learned from your mentorship, which will forever remain a major contributor behind my success and achievements. Thank you for choosing me as your first graduate student. I can only hope to be a mentor as involved and supportive as yourself in the future.

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List of Abbreviations

ABAS-II: Adaptive Behavior Assessment System—Second Edition

ADHD: Attention Deficit/ Hyperactivity Disorder

ANOVA: Analysis of Variance

ASD: Autism Spectrum Disorder

ASEBA: Achenbach System of Empirically Based Assessment

CBCL: Child Behavior Checklist Questionnaire

GAC: General Adaptive Composite

HE: High Externalizing

HIE: High Internalizing and Externalizing

LIE: Low Internalizing and Externalizing

LE: Low Externalizing

NDD: Neurodevelopmental Disorders

OCD: Obsessive Compulsive Disorder

Declaration of Academic Achievement

This research project was devised by Dr. Stelios Georgiades, Dr. Eric Duku, and me. With the help of Michael Chalupka, we received permission to extract participant information from the Province of Ontario Neurodevelopmental Disorders (POND) Network database. I completed a thorough literature review on research relevant to the current topic, which was included in the summation of this thesis. My training in using R program language enabled me to complete the exploratory data analyses in this thesis. My research methods, and statistical methods were guided by Dr. Georgiades and Dr. Duku.

In addition to the work summarized in this thesis, a second research project was initiated during the completion of my graduate thesis. Due to a nation-wide lockdown, which forced a pause on all in-person human research projects, my initial project, titled "Identifying Autism Subtypes using Biomarkers of Functional Connectivity and GABAergic Neural Levels", was halted. This project was designed, and guided by Dr. Jenna Traynor, Dr. Geoffrey Hall, Dr. Stelios Georgiades, and me. I oversaw all study related features, including REB submission and approval, data collection, recruitment materials, and management. For this research study, I completed an fMRI training course, and received training to administer the WASI-IV by psychometrist, Irene O'Connor. Data collection for this project was possible with the help of Dr. Noseworthy, and the MRI technologists, at the Charlton Campus, St. Joseph Healthcare Hamilton. Participants were recruited with the help of the McMaster University community, and the POND Network. This work is not included in this thesis.

Internalizing and Externalizing Problems in Children with ASD, ADHD, and OCD: Identifying Behavioural Profiles Within and Across Diagnostic Categories

Introduction

Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Obsessive-Compulsive Disorder (OCD) are childhood-onset neurodevelopmental disorders (NDDs) associated with significant distress and economic cost to affected individuals, their families, and society (Buescher, et al., 2014; Olesen, et al., 2012). Emerging evidence suggests that there is both within-disorder heterogeneity and across-disorder overlap in the clinical presentation of children with these NDDs with a wide range of comorbidities – from 30 to 80% – being reported by different studies (Brereton et al., 2006; Gadow et al., 2009; Zandt et al., 2009; Rommelse et al., 2010; Lichtenstein et al., 2010; Antshel et al., 2016). Recent genetic and neuroimaging findings show that the three NDDs also share some biological variation, lending support to the idea of possible cross-disorder causal factors and mechanisms (Lichtenstein et al., 2010; Lionel et al., 2011; Jacob et al, 2009; Ronald et al., 2010; Brem et al, 2014; Van der Plas et al., 2015; Ameis et al., 2016; Palumbo, et al., 1997).

Overlap of Diagnostic Categories

Researchers have placed emphasis on investigating the overlapping characteristics across ASD, ADHD, and OCD, due to the increased awareness of the related distress and functional impairment these diagnoses contribute to everyday activities (Halvorsen, et al., 2019; Larson, et al., 2011; Herring et al., 2006). Existing literature demonstrates genetic, behavioural, and neural overlap between these NDDs. ASD and OCD both exhibit similar repetitive behaviours and routines, shared polygenic risk, and similar fronto-striatal connectivity (Ruta, et al., 2010; Guo et al., 2017; Fuccillo, 2016; Voon et al., 2015). High comorbidity rates between ADHD and ASD are partially explained by genetic research, which reveals that there is a 50 to 72% of overlapping genetic factors, and shared deficits of executive function, social cognition, and motor speed (Satterstrom et al., 2019; Stergiakouli et al., 2017; Lichtenstein et al., 2010; Rommelse et al., 2010). In one study, 72% of children with ASD, aged 5 to 17, had at least one additional psychiatric disorder, and amongst the most common were OCD (37.5%), and ADHD (30.6%; Leyfer et al., 2006; Ivarsson & Melin, 2008). Another study reported that rates of internalizing behaviours, such as anxiety and mood problems, are three times the population rate among those with higher functioning ASD (Kim et al., 2000). The high prevalence of overlapping symptomology and other mental health problems is explored across a large number of studies, supporting the ongoing need for a holistic approach in diagnostic processes and intervention strategies (Simonoff, et al., 2008; Larson, et al., 2011; Halvorsen et al., 2019).

In a study conducted by Anholt and colleagues (2010), 109 adult outpatients with a primary OCD diagnosis reported higher scores on ADHD and ASD symptoms than 87 healthy controls. A total of 25 OCD participants were identified as displaying ADHD symptoms suitable for a diagnosis. When compared to the rest of the sample of 84 OCD participants who displayed no signs of ADHD symptomology, OCD participants with ADHD symptoms had a higher total score on the Autism-Spectrum Quotient (AQ), a measure developed to rate autism symptoms; this includes skills such as communication, social skills, and attention switching. Moreover, ASD and ADHD symptoms were shown to share commonalities with OCD dimensions (Anholt, et al., 2010). This phenotypic overlap was replicated in other studies, which demonstrate that OCD participants show increased cognitive impulsivity and impaired decision making, which are symptoms associated with ADHD (Patros et al., 2017; American Psychiatric Association, 2013). The increasing evidence of overlapping characteristics across neurodevelopmental disorders, and the heterogeneity we see within these disorders, supports the need for further cross-disorder investigations to identify homogeneous profiles within and across diagnostic categories.

Internalizing and Externalizing Behaviours in NDDs

Two prevalent dimensional phenotypes in children with NDDs that warrant close attention and are suitable for cross-disorder investigation are internalizing and externalizing problems, sometimes referred to as emotional and behavioural problems. Achenbach (1966) describes internalizing and externalizing psychopathology as being two higher order factors of covarying problems. He describes internalizing problems as problems within the self (i.e., withdrawn behaviour, anxiety, and somatoform symptoms), whereas externalizing problems are described as being a conflict with the environment (i.e., attention, aggression, rule breaking; Achenbach, 1991). A large body of literature suggests that these problems often impair functioning, influence response to treatment, and further complicate the already heterogeneous clinical picture of NDDs (Murray et al., 2015; Noordhof et al., 2015).

The distinction between externalizing and internalizing problems has been validated and replicated in various studies in clinical and general adult and child populations providing a basis for describing heterogeneity and comorbidity of a wide range of problems (Achenbach, 1991; Achenbach, 1966; Noordhof, et al, 2015, Krueger, 1999; Lahey et al., 2008; Markon, 2010; Lahey et al., 2012; Krueger & Markon, 2011; Hasting, 2015; Achenbach et al., 2016). The Child Behaviour Checklist (CBCL) is a widely used psychopathology measure that reports children's problems on internalizing and externalizing scales (Achenbach & Rescorla, 2001). These two dimensions have been validated in confirmatory factor analyses as being distinct, with withdrawn behaviours, anxiety and somatoform symptoms falling within the internalizing category, and delinquent and aggressive behaviours falling within the externalizing category (Achenbach & Rescorla, 2001).

ASD, OCD and ADHD are heterogenous disorders with common underlying biological, and behavioural patterns, including externalizing and internalizing problems persisting across all diagnoses (Baribeau et al., 2019). Studies have shown that externalizing and internalizing problems are not specific to any given diagnostic category; rather, they represent a set of "broadband" phenotypes evident, at variable levels and constellations in children with NDDs, but also in typically developing children (Hudziak et al., 2007; Pandolfi & Magyar, 2014; Geller et al., 2004). One study shows that the co-occurrence of internalizing and externalizing problems is more severe amongst preschool children in comparison to healthy controls, and that one in five ASD participants struggled with clinically elevated internalizing problems that persisted for three years (CBCL T score > 70) (Vaillancourt et al., 2016). Another study, conducted by Bölte, Dickhurt, & Poustka (1999), reported that children with ASD score higher on the mean total score of the CBCL and are at an elevated risk for internalizing and externalizing psychopathology when compared to age matched children in typically developing groups; findings that have been replicated by various studies (Duarte et al., 2003; Stewart et al., 2006; Hartley et al., 2008; Sikora et al., 2008; Sukhodolsky et al., 2008; Bauminger et al., 2010; Yorke et al., 2018). Similar findings have been reported in ADHD and OCD, particularly in children and adolescents, however this is a phenomenon which has been studied to a lesser degree (Pliszka, 1998; Connor et al., 2003; Bauermeister et al., 2007; Gau et al., 2010; Yoshimasu et al., 2012; Armstrong et al., 2015; Kuja-Halkola et al., 2015; Factor et al., 2016; Fogleman et al., 2018, Peris et al., 2008; Storch et al., 2008; Lack et al., 2009; Canavera et al., 2010; Langley et al., 2010; Storch et al., 2010).

The internalizing/externalizing contrast in the application of children's mental health is useful for personalizing intervention plans. A meta-analysis which examined therapies completed on children and adolescents identified as being high risk of behavioural problems, reported that therapy with a specific internalizing or externalizing behaviour focus has more than twice the effect size on the problems on which it focused (Cohen's d = 0.52), than it did on problems on the other dimensions (Cohen's d = 0.22), providing early evidence that focus on internalizing or externalizing problems can affect children's treatment outcomes (Weisz et al., 1995). Other research has demonstrated the ability to utilize the CBCL for early detection of emotional and behavioural problems in preschool aged children, a predictive tool that could be used to subgroup and evaluate NDD outcome trajectories (Irwanto et al., 2019). In recent literature, the CBCL has been utilized as an informative tool for subtyping within NDDs and in applied settings. For example, using the CBCL dimensions, emotional trait profiles were identified between verbal and nonverbal ASD populations and within an ADHD population (Fok & Boy, 2019; Karalanas et al., 2018). However, to our knowledge, transdiagnostic studies of internalizing and externalizing problems in clinical samples of children with NDDs are sparse. The goal of the current study is to elaborate on these approaches by expanding the inclusion population to three NDDs, namely ASD, ADHD, and OCD, and utilize the CBCL to subgroup based on the two phenotypic dimensions, internalizing and externalizing problems.

Diagnostic and Classification Methods

Historically, our nosological models (Diagnostic and Statistical Manual – DSM & International Classification of Diseases – ICD) have conceptualized these three NDDs as mutually exclusive entities. Until DSM 5, a diagnosis of ASD precluded a diagnosis of ADHD, for example (American Psychiatric Association, 2013). These diagnostic systems used observable signs and symptoms to develop an oversimplified common language for diagnostic boundaries, without consideration of pathophysiology or treatment responses (Insel, 2014). As a result, research to date has relied primarily on this categorical approach that did not adequately capture the clinical presentation of affected children, especially those exhibiting more complex, cross-disorder symptom profiles (Kraemer, 2007). The use of a simplistic (yet practical for communication purposes) unidimensional approach for the study of heterogeneous, interrelated disorders may explain (to some extent) our inability to identify valid and reliable biomarkers in NDDs and offer more personalized intervention plans.

To disentangle the heterogeneity amongst diagnostic disorders, identifying subgroups within and across diagnostic categories is an approach to promote targeted etiology studies and effective type-specific intervention. Cluster analysis is a data-driven technique that can be used to derive subgroups, using commonly shared characteristics (i.e., phenotypes). In contrast to traditional clinical methods, which derive descriptive behavioural associations from outcome diagnoses, the clustering approach assigns, empirically, individuals into distinct subgroups determined by shared behavioural characteristics. A diagnosis-agnostic classification approach provides insight on what behavioural profiles overlap with, or are unique to, diagnostic groups. Inclusion criteria for clusters exclusively relies on common characteristics, a grouping method which could enhance our understanding of differential treatment effects (Hair et al., 1998; Lanza & Rhodes, 2013) This technique aims to maximize homogeneity *within* subgroups, while simultaneously maximizing heterogeneity *between* subgroups (Hair et al., 1998). By using similar behavioural symptoms to determine subgroups, this methodological approach seeks to provide insight on empirically disentangling heterogeneity of data across these NDDs.

Study Objectives

This study uses a data-driven, diagnosis-agnostic approach to disentangle the phenotypic heterogeneity in children with ASD, ADHD, and OCD. Specifically, the study uses data on the CBCL Internalizing and Externalizing subscales to derive homogenous clusters that may describe behavioural profiles within and across these three neurodevelopmental disorders. Empirically derived groups are characterized using measures of adaptive functioning and are interpreted in relation to original diagnostic categories.

Methods

Participants

Data came from the Province of Ontario Neurodevelopmental Disorders (POND) Network, a multi-center research network focused on understanding biological underpinnings of neurodevelopmental disorders to improve long-term outcomes for children. A total of 1565 participants were included from a database of 2904 children, from four Centers in Ontario, Canada (Holland Bloorview Kids Rehabilitation Hospital, Toronto, The Hospital for Sick Children, Toronto McMaster Children's Hospital, Hamilton, and Lawson Health Research Institute, London) were included in our analysis. Participants were included in the current study if they were between 6 and 18 years of age and had a primary clinical diagnosis of ASD, ADHD, or OCD. Participants were included on the basis of complete syndrome scale scores on the Child Behaviour Checklist 6-18 (CBCL 6-18). Participants were recruited into the study based on their primary psychiatric diagnosis. The sample includes 417 female participants (27%; Mean age = 11.06 years), and 1148 male participants (73%; Mean age = 10.66 years). A total of 689 participants had a primary diagnosis of ASD (44%, Mean Age = 11.02 years), 647 ADHD (41%, Mean Age = 9.98 years), and 229 OCD (15%, Mean Age = 12.21 years).

Assessment Instruments

The Child Behaviour Checklist (CBCL) is an established 113-item questionnaire used to assess behavioural and emotional problems in children and adolescents. There are two existing versions of the CBCL, one for preschool aged children, and one for youth ages 6 to 18. For our analyses, only the youth aged CBCL measure was included. As part of the Achenbach System of Empirically Based Assessment (ASEBA), the CBCL uses parent/caregiver report in eight scales/domains that capture different aspects of behaviour. There are also two broad subscales made up of these domain scales; the Internalizing Behaviour subscale, which includes the anxious/depressive, withdrawal/depressive, and somatic complaint domains, and the Externalizing Behaviour subscale, which includes rule-breaking and aggressive behaviour domains. The domains comprising the Internalizing and Externalizing scales were included in our analyses, and the three remaining subscales, namely attention problems, thought problems, and social problems, were excluded due to their overlap with core-defining diagnostic components (Achenbach & Rescorla, 2001).

To characterize the study sample, adaptive behavioural skills were quantified using the Adaptive Behavior Assessment System—Second Edition (ABAS-II). The

ABAS-II is a norm-referenced behavioural tool completed by a parent/caregiver. This questionnaire assesses adaptive skills across the life span by assessing eleven skill areas, which are combined to form an all-encompassing General Adaptive Composite (GAC), and three specific domain composites, named Conceptual (communication, functional academic, and self-direction skills), Social (leisure and social skills), and Practical (self-care, home living, community use, and health and safety; Lopata, et al., 2013). To capture adaptive functioning across empirically derived clusters, scores on the GAC and the three adaptive domains were compared across clusters. Adaptive functioning scores were also analyzed across original diagnostic groups to relate adaptive functioning within and across diagnostic labels.

Statistical Analyses

Statistical analyses were performed using R version 4.0.3 (R Core Team, 2020). As a preliminary analysis, we tested the degree to which scores on the CBCL can be explained/predicted by primary diagnostic labels. Linear regression analyses were used to estimate the percentage of variance within CBCL total, and subscale scores accounted for by diagnostic labels, treating primary diagnosis (ASD, ADHD, and OCD) as the categorical predictor variable.

Boxplots (also known as box-and-whisker plots) were used to examine the distribution and range of total, subscale, and individual domain scores across primary diagnostic groups. Boxplots provide a graphical summary based on the quartiles of the data, indicating the location of the median, and where the data is most compact and disbursed. This will depict the distributions and overlap of CBCL total, and subscale, scores between diagnostic groups.

Clustering Model

Our analysis aimed to yield empirically derived clusters using a data-driven, diagnosis-agnostic approach. Ward's minimum variance hierarchical cluster analysis was performed to identify homogenous clusters based on behavioural profiles, using CBCL Internalizing and Externalizing subscale scores (Ward, 1963). This is an agglomerative clustering method based on classical sum-of-squares criterion, which are not defined a priori, therefore the number of clusters and size of the clusters are not known beforehand. This procedure operates by assigning each individual participant a single cluster and gradually reducing total cluster groups by combining clusters closest to each other to form new clusters. Cluster membership is determined by square Euclidean distance, to maximize between-cluster variance relative to within-cluster variance.

The dendrogram, produced from the Ward's analysis, and a scree plot (elbow plot) were used for visual analysis of the agglomeration of scores to determine an appropriate number of clusters to test. The scree plot shows the number of clusters generated by the analysis on the x-axis and displays the total within sum of squares on the y-axis. The point at which the slope of the curve is levelling off indicates the number of clusters most appropriate to use. Decisions on the number of clusters to test in the k-means analysis (see below) were based on consideration of the dendrogram, the scree plot, and conceptual interpretation of derived clusters.

K-means cluster analysis is a non-hierarchical clustering approach that minimizes within-class sum of squares for a given number of clusters. This algorithm establishes clusters by assigning random data points as cluster centers, and as each observation is evaluated and placed in a cluster, the centers are updated until the cluster centers no longer move. This analysis requires trialing several “k” number of clusters, and the solution minimizes the total error sum of squares criterion. K-means clustering minimizes the within group dispersion and maximizes the between-group dispersion. The groups for k-means partitioning are informed by the hierarchical Ward’s clustering analysis, which determines appropriate numbers of clusters that fit the data, and the non-hierarchical k-means analysis determines the stability of this cluster membership (Hair & Black, 2000). K-means analyses report a value of within-cluster sum of squares per cluster, which is a measure of the variability of the observations within each cluster. In general, a small sum of squares value indicates that a cluster is more compact than a cluster that has a large sum of squares. Greater variability of the observations within the cluster are expected in clusters that have higher values.

Cluster Characterization

After a cluster solution is chosen from the k-means analyses, a series of additional analyses were performed to characterize the clusters. Cluster groups were initially compared for size, mean age, and gender ratio. Mean scores across CBCL Internalizing and Externalizing subscales were then computed and plotted to characterize the behavioural profiles of each cluster. Patterns in these findings were used to establish cluster-specific behavioural profiles. A plot of the clusters was drawn to demonstrate the range and distribution within and between the derived clusters. To determine if these derived clusters significantly differed, CBCL total scores were compared between clusters. Boxplots and Mean plots provided a visual presentation of the distribution of CBCL total scores between clusters. A One-way ANOVA was conducted as a statistical comparison, to verify whether derived clusters significantly differ, by comparing CBCL total scores. To further characterize the empirical groups, domain-specific scores on the ABAS-II were used to characterize clusters by level of adaptive functioning. Means on GAC, and the three domain composite cores, were plotted for comparison of patterns between clusters. Finally, original diagnostic labels were used to analyze how diagnostic groups distributed across derived cluster groups.

Clusters in Relation to Diagnostic Labels

To better understand how the empirically derived subgroups relate to primary diagnostic labels, the mean scores of primary diagnostic groups were compared by cluster group. Participant’s primary diagnostic label decided their inclusion in either the ASD, ADHD, or OCD group. Before comparing means, the distribution of cluster groups within diagnostic groups, and vice versa, was examined; this provided insight on whether the derived clusters are capturing the heterogeneity across diagnostic groups. To detect whether empirically derived clusters reveal different behavioural or adaptive functioning patterns than participant's original diagnostic groups, both classifying groups (diagnosis and derived clusters) were compared across scores of measures from the two assessments: CBCL and ABAS-II. The mean scores on the CBCL's Internalizing and Externalizing subscale domains were plotted to represent diagnostic groups' mean scores on each domain, which was then compared to the derived cluster's plotted scores. Next, adaptive functioning scores were compared by primary diagnostic group and by clusters. Mean scores for GAC, Social, Practical, and Conceptual domain composites on the ABAS-II were plotted for each diagnostic group and then compared by derived cluster results.

Results

Preliminary Analyses

Results from linear regression model suggest that all CBCL scores cannot be sufficiently explained/predicted by the three original primary diagnostic labels. When CBCL total T-scores were used as the response variable, and primary diagnosis as the predictor variable, the results demonstrate that there is a significant difference in reported total scores between ADHD and OCD ($p = 4.86e-09$), but not between ADHD and ASD ($p = 0.725$). The linear regression model calculating CBCL total T-scores is significant ($p = 5.735e-09$), however, this analysis also reveals that primary diagnostic labels only account for 2% (Adjusted R-squared= 0.02276) of the variance in the CBCL total score (*See suppl. Table 1a*).

A linear regression model including only Internalizing subscale domains (anxious/depressed, somatic complaints, and withdrawal/depression domains) demonstrate that ADHD significantly differs from ASD (p = 0.000324), and OCD (p= 8.65e-06), however diagnosis only accounts for 1% of the variability in internalizing domain scores (Adjusted R-squared = 0.01411; *See suppl. Table 1b).* Diagnosis on its own accounts for 3% of the Anxious/Depressed domain score (Adjusted R-squared: 0.036), and 5% of the Withdrawal/Depression domain score (Adjusted R-squared = 0.052), but only 0.7% of Somatic Complaints domain score (Adjusted R-squared = 0.007; *See suppl. Table 2*) .

When accounting for only Externalizing subscale domains (rule-breaking and aggression domain), the linear regression model reveals that ADHD significantly differs from ASD (p = 5.11e-10), and OCD (< 2e-16*)*. However, diagnosis only accounts for 6% of the variability in externalizing scores (Adjusted R-squared= .06447; *See suppl. Table 1c*). Separately, diagnosis accounts for 7% of the variability in Rule Breaking Domain (Adjusted-R squared = 0.071), and 4% of Aggression (Adjusted R-squared= 0.046; *See suppl. Table 2*). These findings suggest that diagnostic categories did not account for the variability captured in the CBCL, therefore supporting the need for empirically derived clusters.

Boxplots were used to examine the visual distribution of CBCL total composite scores, as well as total subscale and subscale domain scores across diagnostic labels. As shown in *Figure 1a*, there are no significant differences between ADHD and ASD on total composite scores, however OCD scores are relatively lower. Externalizing scores are also highest amongst the ADHD group, and lowest amongst the OCD group, a difference that was not evident across internalizing subscale scores. Across all boxplots in *Figure 1*, the ADHD group consistently demonstrates a greater range of scores; this may be indicative of the group's heterogeneity in internalizing and externalizing behaviours/problems.

Selecting Optimal Cluster Solution

Ward's minimum variance hierarchical cluster analysis show that the optimal cluster solution is somewhere between 2 to 5 cluster groups. A dendrogram, from the Ward's analysis, demonstrates a top-down visual of the clustering progression within the data (*See Figure 2*). This dendrogram reveals two distinct cluster groups, with possible cluster solutions of up to five groups. As seen in the scree plot in *Figure 3*, the total within sum of squares begin to level off at approximately x = 4, indicating that this may be an optimal cluster solution.

K-means cluster analyses were used to compare cluster model solutions with k = 1 through 6. *Figure 4* illustrates the results of six different cluster solutions. Clusters in each model are compared on means of the five CBCL domain scores included in the Internalizing (Anxiety/Depression, Withdrawal/Depression, and Somatic Complaints) and Externalizing subscales (Aggression and Rule-Breaking). Based on the CBCL manual, the solid line indicates a score above clinical range, anything between the solid and dotted line indicate borderline clinical range, and anything underneath the dotted line is outside of the clinical range.

Figure 4a, which presents the data with no clusters, reveals that overall, the sample has an average score below the clinical threshold across all domains, with a significant dip in one externalizing domain (Rule-Breaking). *Figure 4b* presents a two-cluster model solution, which shows a split between the two high and low scoring clusters, revealing that a significant proportion of the sample is scoring above the borderline clinical range. The three-cluster model (*Figure 4c*) reveals a more dimensional group that strays from the overall high and low scoring clusters, rather a group with differing internalizing and externalizing behaviour score means. This third cluster averages in the borderline clinical range for internalizing scores and is low on externalizing scores. This distinction in behavioural subscales is also seen in the four-cluster solution *(Figure 4d)*, where an additional cluster emerges. The fourth cluster has mean scores in the mid range for internalizing behaviours, however, is in the borderline clinical range in externalizing behaviours. The results of the five and six-cluster model solutions *(Figure 4e & Figure 4f)* increasingly complicate the separation of behavioural profiles, making these solutions unintuitive and difficult to grasp. Through interpretation of the dendrogram, scree plot, k-means solution results, and conceptual interpretation, the four-cluster model solution was selected as the optimal solution to investigate further.

Behavioural Profiles of Empirically Derived Clusters

A cluster plot analysis was used to analyze the range and distribution of the four-cluster model solution *(Figure 5)*. The cluster plot analysis reveals the four clusters are distinct and compact, with minimal overlap between them. Application of this model solution achieves a reduction of sums of square of 53.2% (between sum of squares / total sum of squares = 53.2%); this is the total variance accounted for in the sample. Age and gender do not significantly differ, with an average age of 10.5 years of age, and a 1:4 ratio of female to male participants in all clusters.

The chosen cluster model solution displays four distinct clusters (*Figure 6*). The first cluster is the smallest cluster (N = 241; 15%) and can be described as the High Internalizing Externalizing (HIE) group, with mean scores at or above borderline clinical range (M total score= 75.6, SD= 4.09). In contrast, the largest cluster (N = 609; 38%), can be described as the Low Internalizing Externalizing (LIE) group, which represents an overall low scoring profile across both subscales (M total score = 55, SD = 6.38). The remaining two groups show mid range internalizing scores, however one cluster (N= 330; 21%) represents children with High Externalizing (HE) scores (M total score = 68.1, SD= 4.09), whereas the last group (N = 404; 26%) represents those with Low Externalizing (LE) scores (M total score = 66.1, SD = 5.43; *See Table 1).*

The derived clusters were compared on CBCL total score. The Boxplot in *Figure 6a* illustrates a modest distribution of scores across all derived clusters. The Mean-plot in *Figure 6b* was used to illustrate the spread of participant data, which confirms the homogeneity of the derived cluster groups. A One-way analysis of variance (ANOVA) was also conducted to compare the means of the derived empirical clusters on CBCL total score *(See Table 2)*. The ANOVA analysis showed that the differences in means of derived clusters on CBCL total score was significant, $F(3, 1561) = 1035$, $p < 2e\text{-}16$. Post hoc comparisons using t-test with Bonferroni correction indicated that the differences in mean scores between the HE and HIE, HE and LIE, and LE and LIE clusters were significant, with a p value < 2e-16. Mean scores between LE and HE were also significant, with a p-value = 2e-06. Taken together, these results suggest that the empirically derived cluster groups are statistically different on CBCL total scores *(Table 2)*.

Adaptive functioning was also used to characterize group differences between clusters, with scores on the ABAS-II *(see Figure 7a)*. Based on the ABAS-II manual, the solid line indicates a norm-referenced score of M = 100, and the dotted lines denote the SD = 15. The aggregated mean on the GAC was plotted alongside the three subscales: Practical, Conceptual, and Social skills. *Figure 7a* reveals that when comparing adaptive functioning, the four clusters split into two patterns: mid or low range. The HIE and HE clusters show lower adaptive functioning scores, whereas the LIE and LE group show mid-range adaptive functioning scores. These findings suggest an inverse relationship between externalizing behaviour and adaptive functioning: high externalizing behavioural scores yield lower adaptive functioning scores. However, no relationship between internalizing behavioural scores and adaptive functioning scores was detected.

Diagnostic Categories Relative to Derived Clusters

The distribution of derived groups within original diagnostic labels, as well as diagnostic groups within derived clusters, was plotted to decipher whether clusters are capturing different attributes of the sample. *Figure 8a* presents a visual of the proportion of individuals that were assigned to each cluster group, HIE, LIE, HI, and LI, within each original diagnostic label.

Conversely, *Figure 8b* reveals the distribution of diagnostic labels within each derived cluster. It is evident in *Figure 8a* that derived clusters are prevalent across all included NDDs, and the LIE and HIE groups show similar proportions across all diagnostic groups. Similarly, *Figure 8b* reveals that all derived clusters are represented within each diagnostic group, and ASD is prominent across all derived groups. *Figure 8a* shows an interesting pattern across the LE and HE groups, where LE is least prevalent in ADHD and most prevalent in OCD, whereas HE is most prevalent in ADHD and least prevalent in OCD. This pattern is also evident in *Figure 8b*, across OCD and ADHD groups: OCD is most prevalent in the LE group, and least prevalent in the HE groups, whereas ADHD is most prevalent in the HE group, and least prevalent in the LE group.

To compare internalizing and externalizing behaviours by diagnostic groups mean scores on the CBCL subscale domains were plotted (*Figure 9*). The diagnostic groups reveal a distinction between groups when comparing mean scores on the Externalizing subscales, which are not present when comparing means on Internalizing subscales. All mean scores remain below the borderline clinical range, except for one Internalizing scale score (anxiety/depressive domain) from the OCD group, which averages above borderline clinical range. The pattern behavioural scores across diagnostic labels differ from the CBCL scores of the derived groups *(Figure 10)*, reinforcing the notion that empirically derived groups are capturing behavioural profiles not detected by diagnostic groups. This is especially true for the HIE and LIE groups, which illustrate distinct behavioural patterns from diagnostic groups.

Adaptive functioning was next evaluated across diagnostic groups. *Figure 7b* reveals that diagnostic groups had distinct levels across adaptive functioning scores, with OCD displaying highest adaptive functioning, and ASD displaying lowest adaptive functioning. These results mirror the pattern shown in the externalizing subscales in the CBCL analysis *(Figure 9)*, however diagnostic groups are organized in a different order. This graph remains distinctly different from the adaptive functioning scores of the derived clusters *(Figure 7a)*. On average, all cluster mean scores were low, whereas there was larger variation in mean scores across diagnostic groups. These results suggest that diagnostic labels are capturing different adaptive functioning characteristics (albeit less variability) than the derived clusters, therefore are uniquely useful in capturing phenotypic profiles.

Discussion

In this study, we used a data-driven, diagnosis-agnostic, approach to examine phenotypic heterogeneity *between* and *within* ASD, ADHD, and OCD. The use of dimensional phenotypes (CBCL syndrome scales) that “cut across” conventional diagnostic categories presents a promising, informative way of classifying children into subgroups based on empirically derived (data-driven) profiles. The purpose of this study was to use behavioural phenotypes to identify whether distinct behavioural profiles exist across these primary diagnostic categories. Overall, our results suggest that the heterogeneity in internalizing and externalizing behavioural problems is not sufficiently accounted for by existing diagnostic categories (ASD, ADHD, OCD) and therefore empirically derived subgroups could add to our understanding of behavioural profiles in children with these three NDDs.

Behavioural Problems and Diagnostic Categories

Our preliminary analyses revealed that primary diagnostic labels cannot sufficiently account for the variability seen across CBCL subscale domains. This means that knowledge of one's diagnostic label (ASD, ADHD, OCD) alone may not be sufficient in explaining/predicting externalizing and internalizing behaviour problem patterns. Traditional diagnostic labels are not accounting for the valuable information gathered by the CBCL, which amounts to insufficiently capturing the entire scope of an individual's behavioural challenges, resulting in important needs being neglected or not met (Cunningham & Ollendick, 2010). The derived empirical clusters presented in this study account for approximately half of the variability across both CBCL subscales, suggesting that externalizing and internalizing problem behaviours are being more accurately accounted for through consideration of derived clusters, compared to diagnostic labels alone. Combining empirically derived clusters, with established diagnostic labels, would more dynamically capture individual needs.

Children who receive a diagnosis of ASD, ADHD, or OCD are often treated with different treatment plans, however the overlap across these NDDs is especially prevalent in phenotypic expression. For example, studies have shown that individuals who show both ADHD and ASD symptoms express autistic symptoms more strongly but show similar emotional and behaviour deficits as ADHD only groups (Sprenger et al., 2013; Craig et al., 2014). Moreover, studies show that ADHD symptoms moderate the expression of ASD’s cognitive and behavioural phenotypes by exacerbating impairments (Yerys et al., 2009). Identifying phenotypic expressions that cut across these NDD labels could help disentangle the heterogeneity that has hindered our ability to offer more effective, individualized treatment. A systematic way of classifying behavioural phenotypes, by identifying internalizing and externalizing behavioural problems, could contribute to transdiagnostic treatments that identify the overlapping symptoms of these NDD diagnostic groups.

Behavioural Profiles of Empirically Derived Clusters

To capture the dynamic phenotypic profiles across our NDD sample, empirical clusters were derived using a four-cluster model solution determined posteriori by informed cluster analyses. These derived groups display unique combinations of externalizing and internalizing behaviour profiles that are statistically and conceptually distinct from one another. A cluster that may warrant more clinical attention is labelled the High Internalizing-Externalizing (HIE) group, with mean scores ranging between borderline clinical and clinical ranges across both subscales. This group is the smallest of the four clusters, however critical because this group is likely to require the most targeted intervention and clinical care. For example, studies suggest that co-occurrence of internalizing and externalizing problems is associated with heightened developmental risk, which persists across development (Fanti & Henrich, 2010; Capaldi & Stoolmiler, 1999; Boylan, Vaillancourt & Szatamari, 2012) In contrast, the largest cluster group is best described as the Low Internalizing-Externalizing (LIE) group, which has the lowest risk because this group displays low scores across both CBCL subscales. The last two groups show mid-range internalizing subscale scores, however, vary in scores across the externalizing subscale. The High Externalizing (HE) group shows mid to low internalizing scores, which is contrasted with borderline clinical range scores in externalizing domains. In contrast, the Low Externalizing (LE) group displays mid to borderline clinical range scores on internalizing domains, and lower scores on the externalizing domains.

The results of the present study are parallel to those reported by Vaillancourt et al., (2016), who examined the joint development of internalizing and externalizing behaviours on a sample of 392 ASD children aged 3 to 15 tears, across a two-to-four-year time span. This study’s findings describe five distinct behavioural profiles; four of which are similar to the clusters derived in the current study. Vaillancourt et al., describes the largest group (41%) as a low-risk group that depicts declining internalizing and externalizing problems, with a similar frequency as the LIE group in the current study (38%). A second group shows distinct patterns of maintaining low declining internalizing scores, and moderately declining externalizing scores, and a third shows high/stable internalizing and moderate/declining externalizing problem group, which are similar to the patterns found in our HE and LE groups. Most importantly, the HIE group, which is the most high-risk group identified in our findings, is comparable to the High/Stable internalizing and externalizing group in this research study. Although this research only included an ASD sample, the replicability of similar groups across NDD samples, may suggest some validation for the use of the current study's empirically derived clusters.

Study findings suggest no differences in the distributions of age and gender across all derived clusters, however, a distinction was revealed in adaptive functioning scores. The LE and LIE groups score higher in adaptive functioning than the HE and HIE groups, suggesting that externalizing behaviours are inversely related to adaptive functioning. Conversely, similar findings were not found between internalizing behaviours and adaptive functioning, revealing no relationship. Early childhood externalizing behavioural problems have been shown to predict adaptive functioning in early adolescence, which are mediated by internalizing behavioural problems, and late childhood adaptive functioning (Bornstein et al., 2013). Therefore, accurately describing a child's internalizing and externalizing behavioural profile in early childhood could promote the necessary intervention treatments to promote adaptive functioning skills for later life.

Derived Clusters in Relation to Diagnostic Groups

To determine whether the derived groups presented in this study capture distinct characteristics that that cut across conventional diagnostic labels, several comparative analyses were conducted. Findings show that the ASD sample is captured in all derived clusters, despite their distinct behavioural profiles, emphasizing the heterogeneity of the ASD diagnostic group (Yorke et al., 2018). Although ADHD was prevalent in all four clusters, it is most prevalent in clusters with higher externalizing scores, which are findings that have been replicated in literature (Yerys et al., 2009; Craig et al., 2014). OCD is most prevalent in the low externalizing clusters, supporting evidence that shows that there is a primary focus on cognitive impairments across effected individuals, however the OCD group was represented across all derived clusters (Storch et al., 2008). These findings demonstrate that derived clusters are capturing phenotypic characteristics beyond diagnostic criteria, emphasizing the need for understanding the within-group heterogeneity across all diagnostic groups (Baribeau et al., 2019; Kushki et al, 2019).

To establish that diagnostic groups are capturing different characteristics than derived clusters across this NDD sample, means on Internalizing and Externalizing CBCL subscales were plotted for ASD, ADHD, and OCD groups. The results shown in *Figure 9* reveal a very different set of groups than the derived clusters on the same measure (*Figure 10*). Comparing these graphs reveals that the use of diagnostic categories alone may be masking important, distinct patterns of externalizing and internalizing behaviour problems in children with ASD, ADHD, and OCD. The averaging of scores across the three NDDs eliminates the LIE group, which is the largest group amongst the derived clusters. Another concerning element is the inaccurate representation of all individuals having scores below clinical or borderline thresholds. The derived clusters reveal that a substantial proportion of children with NDDs display close to or above borderline clinical internalizing and/or externalizing scores, something that is not represented when averaging behavioural scores across primary diagnostic groups. Perhaps more importantly, the HIE group, which encompasses participants from all three NDDs, is entirely indistinguishable if we only use primary diagnostic groups. This is problematic because individuals with comorbid internalizing and externalizing behaviours reveal remarkably high continuity in comorbid symptom profiles, which reduces a child's overall developmental well being when early prevention and intervention efforts can reduce behaviour problems (Narusyte et al, 2017; Willner et al, 2016). Using diagnostic group averages to explain/predict behavioural profiles is concerning because none of the derived clusters is captured by the diagnostic group patterns. Using only diagnostic groups to predict projected behaviour problems inaccurately represents all affected individuals, therefore being able to identify behavioural profiles beyond diagnostic labels would promote identification of behavioural challenges and needs. These findings highlight the heterogeneity within disorder that often leads to over generalized clinical application and intervention solutions. Additional information about behavioural profiles may help clinicians better document the specific needs of diagnosed individuals (Cunningham & Ollendick, 2010). By identifying various profiles of internalizing/ externalizing problems, interventions can be better curated on a unique individual basis, without neglecting either problem area.

To further examine the potential utility of the empirically derived clusters, adaptive functioning scores were compared. Clusters were compared on a General Adaptive Composite, as well as the three subscales: Practical, Conceptual and Social domains. As seen in *Figure 7b*, diagnostic labels demonstrate a three-tier pattern between the diagnostic groups, with ASD scoring lowest, and OCD scoring high across all composite scores. This is a contrast to the findings shown in *Figure 7a*, where clusters seem to be influenced by externalizing behavioural problems. Externalizing behaviours also influence the rate at which a diagnostic group appears in our study's derived clusters. As seen in *Figure 8a* and *Figure 8b*, individuals diagnosed with ADHD are more likely to appear in high externalizing groups (HIE & HE), and those with a diagnosis of OCD are more likely to appear in low externalizing groups (LIE & LE). What this may suggest is that externalizing behaviours are carrying more weight in the decision-making process related to diagnosis, while internalizing behaviours are overshadowed. Researchers who have investigated internalizing and externalizing behaviours have reported similar findings. For example, Turygin and colleagues (2013) found that externalizing scores were more severe amongst ASD groups, however no differences were detectable in internalizing behaviour scores across individuals diagnosed and not diagnosed with ASD (Turygin et al., 2013).

Diagnostic labels are useful tools to direct clinical intervention and predict prognosis, however the enormous variability within diagnoses may be masking individual differences and unique clinical needs of children with differing behavioural profiles (Cunninham & Ollendick, 2010; Baribeau, 2019). The findings of this study suggest that more detailed examination of internalizing and externalizing problems may lead to the identification of empirically derived profiles that would promote the use and inform the development of more targeted and personalized intervention plans.

Limitations and Future Directions

Several study limitations need to be considered when interpreting these findings. First, the sample was extracted from a database of 2904 participants, but only 1565 participants were eligible due to inclusion criteria, and missing data, which generates possible selection biases in our sample. Second, the derived clusters presented in this study were only formulated using a single parent-report measure. Parent-report measures are often biased, and may be impacted by social desirability biases. Addtionally, this study used a single behavioural questionnaire to derive cluster groups (CBCL), therefore to determine the validity of these clusters, similar results should be replicated using external validators. For example, future research should examine the presence of behavioural groups using longitudinal data, to see how behavioural profiles persist over time, if at all. Neuroimaging studies could also be beneficial in identifying neural biomarkers that may provide evidence on the validity and possible utility of these emmpirically derived phenotypic profiles.

Another limitation in this study is the sole use of primary diagnostic labels, without the option to investigate the behaviours of participants with comorbid diagnostic labels. Comorbid diagnoses were not recorded in the database that the sample was extracted from, however collecting comorbid results would be an important step to better understand heterogenity across these NDD groups (Antshel et al., 2016; Geller et al., 2004; Simonoff et al., 2008; Waddington et al., 2018).

Although the clustering model approach has promising utility in health research, it comes with limitations. Defined clusters are mutually exclusive, accounting for heterogeneity across clusters, however heterogeneity within the latent groups is overlooked; therefore, all individuals of a single cluster are reportedly expected to demonstrate similar responses and trajectories. Next steps would include implementing a more sophisticated clustering approach, such as Factor Fixture Model (FMM; Lubke & Muthen, 2005). FMM combines factor analysis, used for continous variables, and latent class analysis, used for categorical variables, to capture dimensional groups across and within derived clusters (Lubke & Muthén, 2005; Georgiades et al., 2013). The multi-layered clustering method may generate more informative and clinically useful phenotypic risk profiles (Doyle et al., 2020).

Conclusion

Although conventional diagnostic labels of ASD, ADHD, and OCD may be useful in guiding clinical intervention and predicting outcome, they often are limited in describing individual differences and unique clinical needs related to behavioural problems. Data-driven approaches can inform our understanding of the *between* and *within* phenotypic heterogeneity seen in these neurodevelopmental disorders. By taking a diagnosis-agnostic approach, this study utilized data on the CBCL internalizing and externalizing subscales to derive groups of children who share specific profiles of behavioural problems. This empirical way of classifying children with homogeneous behavioural profiles may complement existing diagnostic models in our efforts to develop more targeted and personalized interventions for children with neurodevelopmental disorders. This more dynamic approach to classification can also help inform our quest for common and unique etiologies across neurodevelopmental spectra.

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Figures and Tables

Sample Characteristics of Derived Clusters

High Externalizing(HE) Group:

	Sample N	Avg. Age	Females	Males
Overall	**330**	**9.86**	**82**	**248**
ASD	130	10.05	29	101
ADHD	187	9.58	45	142
OCD	13	12.15	8	5

High Internalizing-Externalizing(HIE)Group:

	Sample N	Avg. Age	Females	Males
Overall	**240**	**10.43**	**66**	**174**
ASD	93	10.96	20	73
ADHD	116	9.59	32	84
OCD	31	11.97	14	17

Low Externalizing (LE) Group:

	Sample N	Avg. Age	Females	Males
Overall	**399**	**11.42**	**117**	**282**
ASD	199	11.64	42	157
ADHD	103	10.34	27	76
OCD	97	12.11	48	49

Low Internalizing-Externalizing(LIE) Group:

	Sample N	Avg. Age	Females	Males
Overall	**596**	**10.96**	**152**	**444**
ASD	267	11.04	54	213
ADHD	241	10.33	61	180
OCD	88	12.41	37	51

Table 1: Total sample, average age, and gender distrbution across diagnostic labels are shown for the four empirically derived clusters: High Externalizing (HE), High Internalizing-Externalizing (HIE), Low Externalizing (LE) and Low Internalizing-Externalizing (LIE) groups.

Descriptive Statistics of Derived Clusters

a)

Basic Descriptive Statistics

Group	Sample	Mean of CBCL total scores	SD
HE	330	68.1	4.09
HIE	240	75.6	3.3
LE	399	66.1	5.43
LIE	596	55	6.38

b)

One-Way ANOVA Analysis

	Df	Sum Sq	Mean Sq	F Value	Pr(>F)
Group	3	87666	29222	1035	<2e-16***
Residuals	1561	44066	28		
Signif. Codes:		0 '***'	0.001 '**'	0.05 '*'	0.1 ' '

c)

Bonferroni Pairwise Comparison T-test

	HE	HIE	LE
HIE	<2e-06	-	-
LE	2e-06	<2e-16	-
LIE	<2e-16	<2e-16	<2e-16

Table 2: Mean and standard deviations of Child Behaviour Checklist (CBCL) total scores by cluster groups are presented (a). One-way Analyses of Variance (ANOVA) tests reveals that there is a significant difference amongst these cluster groups (b). A conservative pairwise-comparisons of cluster groups, using a Bonferroni adjustment, illustrates that there is a statistical significance between all pairs of clusters (c).

Boxplot of Diagnostic Labels across CBCL Scores

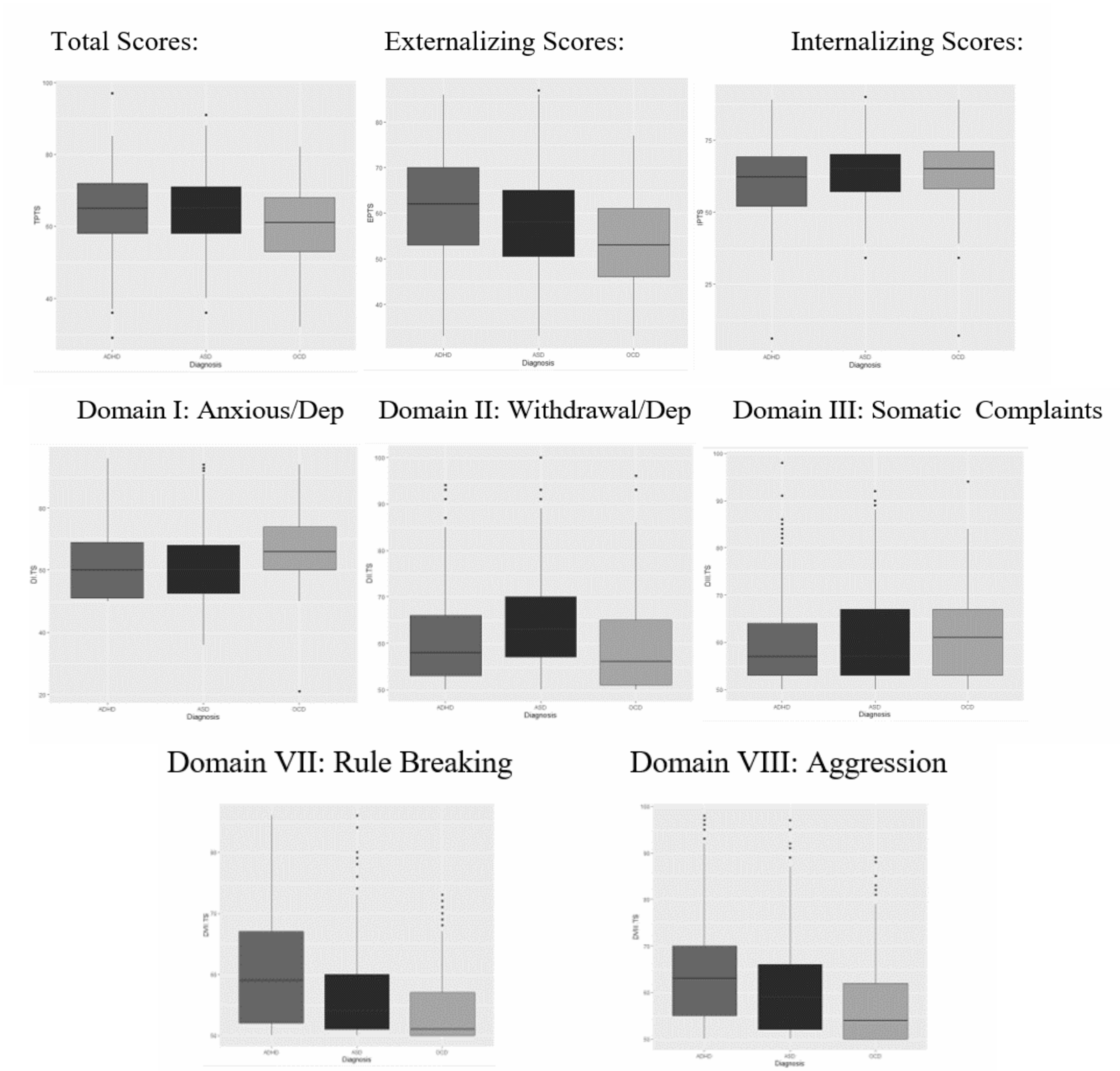


Figure 1: Boxplots are used to compare the distribution of primary diagnostic labels (ASD, ADHD, and OCD) across Child Behavioural Checklist (CBCL) total, subscale, and subscale-domain scores

Cluster Dendrogram

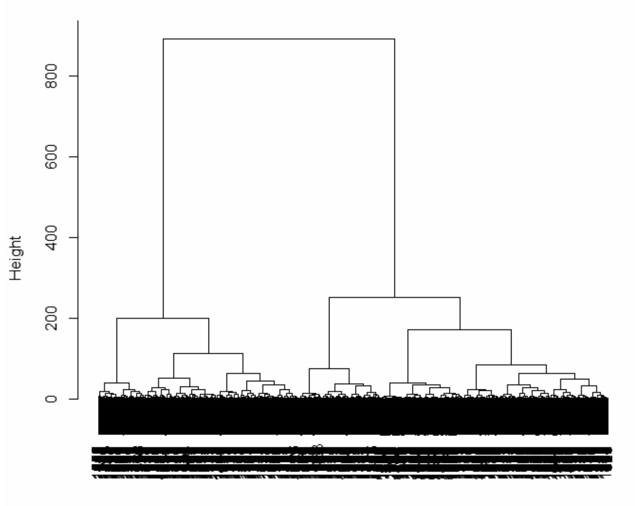


Figure 2: Dendrogram from Ward's minimum variance hierarchical cluster analysis illustrates the possibility of two to five clustering solutions

Scree Plot (Elbow-Plot)

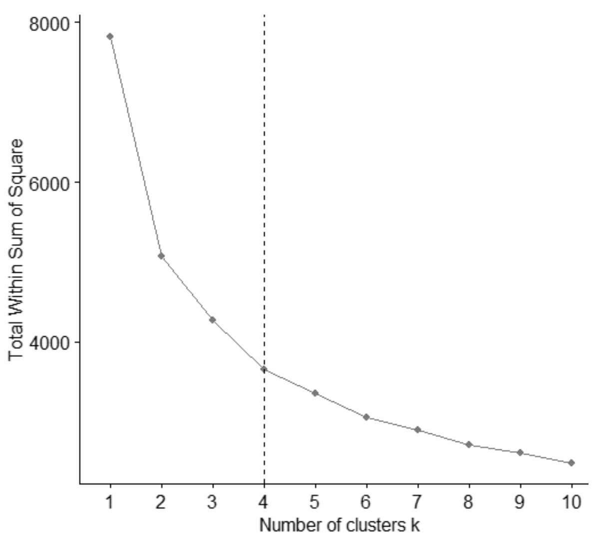


Figure 3: Scree plot analyses were used to determine a best-fit cluster solution. By identifying where the line begins to level off, it is determined that the optimal number of clusters in this sample is four (x = 4).

K-means Analyses: Cluster Solutions 1 through 6

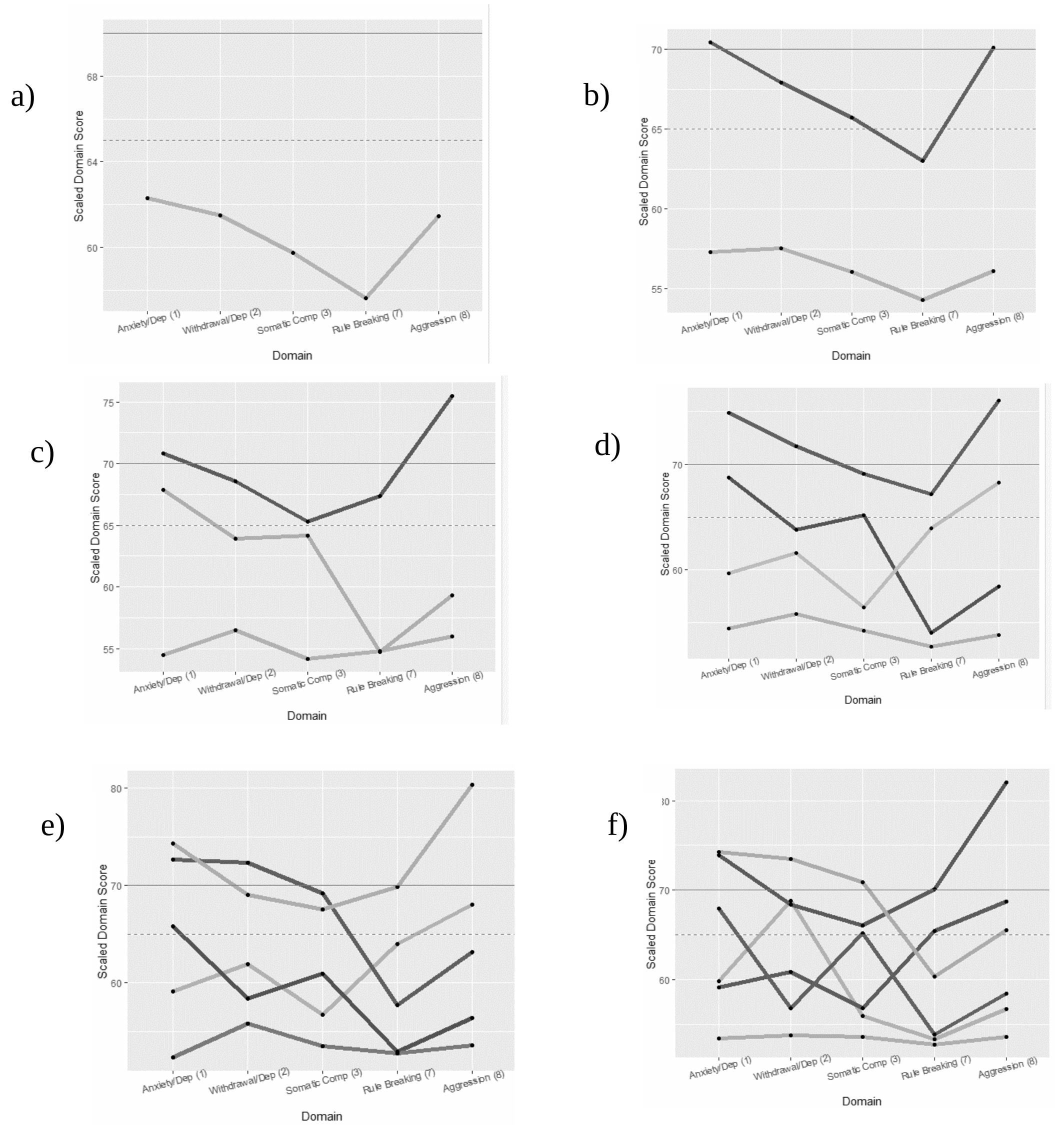


Figure 4: K-means analyses were used to compare cluster solutions of one to six clusters. Mean scores on Child Behaviour Checklist (CBCL) Internalizing (scales 1-3) and Externalizing (scales 4-5) subscales were used to compare cluster patterns across each solution.

Cluster Plot

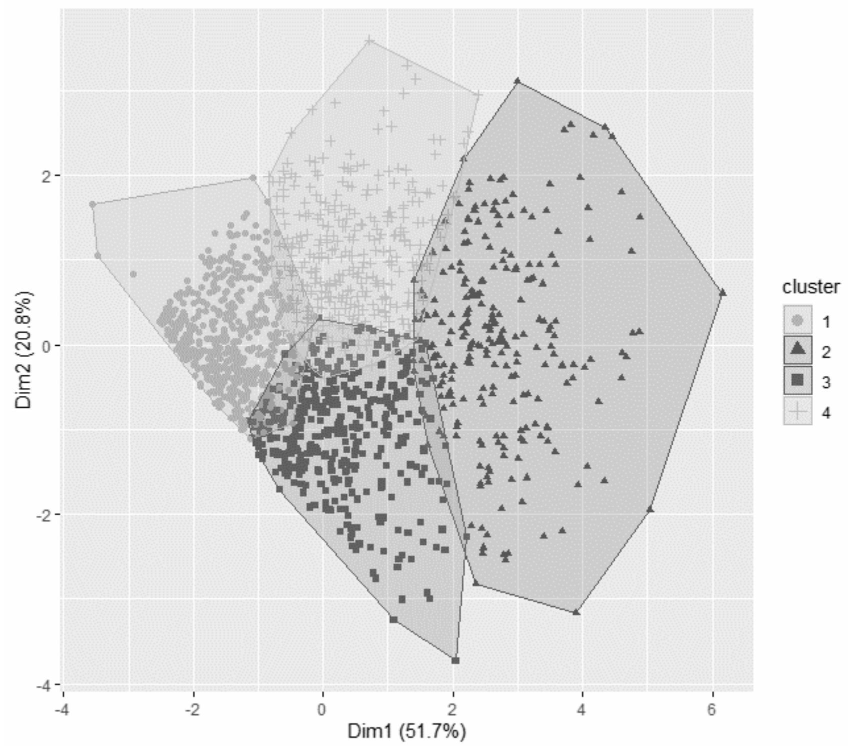


Figure 5: A Cluster plot shows the distribution and overlap of the selected four cluster k-means analysis solution. This provides evidence that the four clusters are distinct, and minimally overlap one another.

Descriptive Data of Derived Clusters

a)

b)

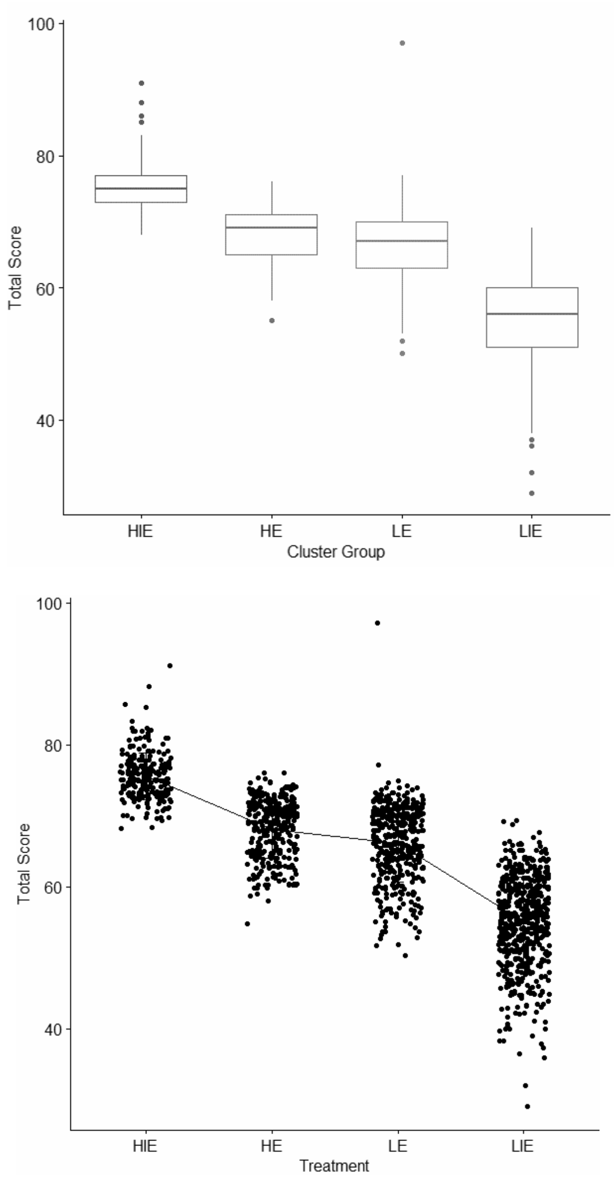


Figure 6: Cluster groups are compared on Child Behavioural Checklist (CBCL) total score. Boxplots illustrate the differences in mean score and range (a), while Mean Plots demonstrate distribution and central tendencies of each cluster (b).

Adaptive Functioning Scores of Derived Clusters and Diagnostic Labels

a)

b)

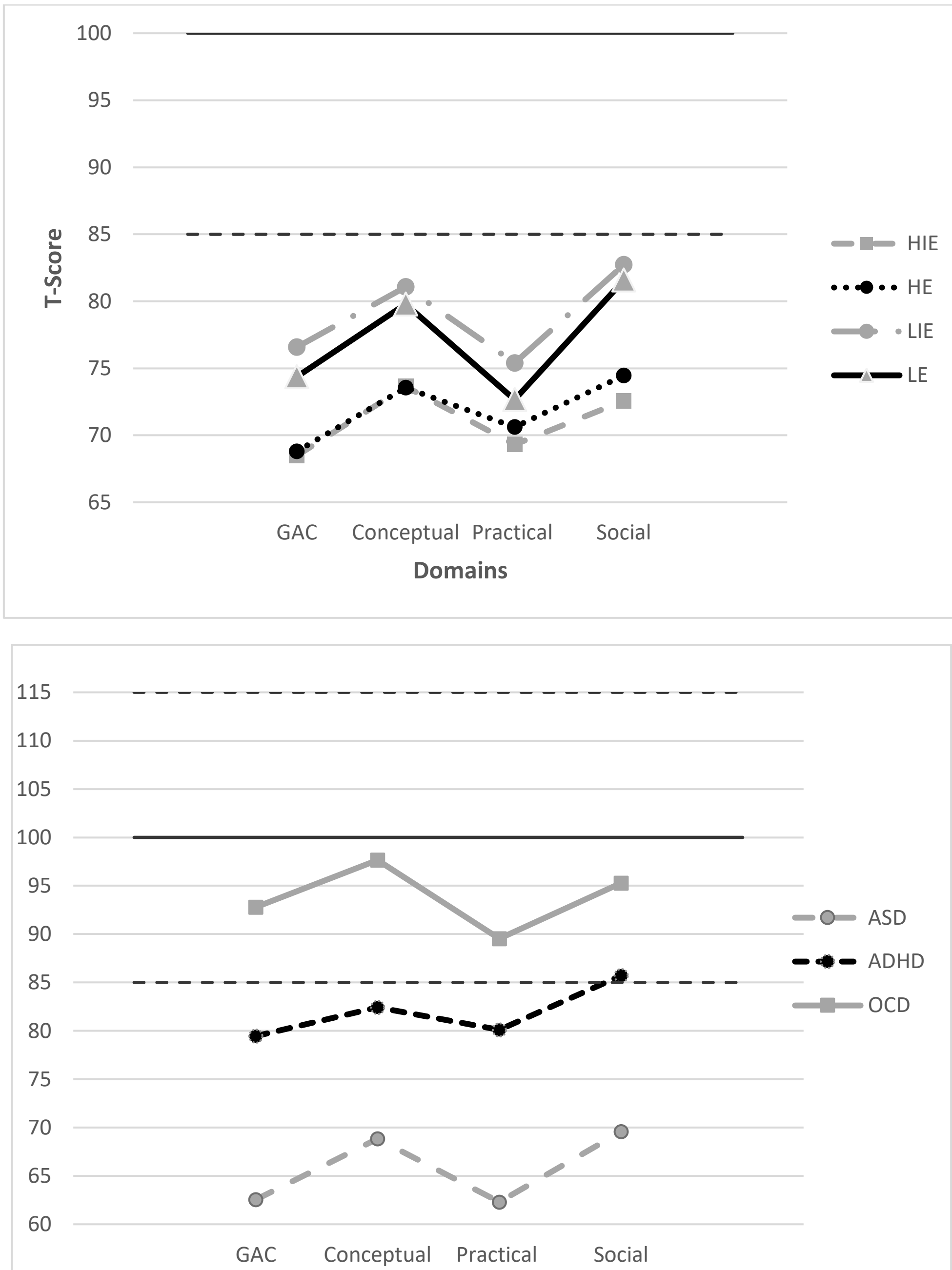
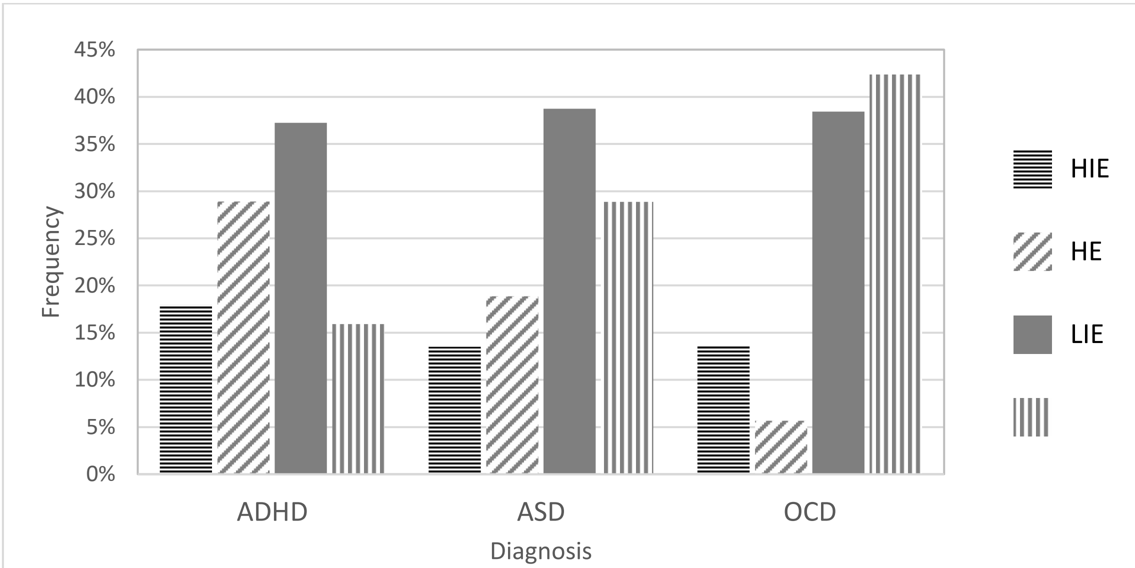


Figure 7: Mean scores on the adaptive functioning measure (ABAS-II) across derived clusters (a) and diagnostic labels (b). The solid line indicates a norm-referenced score (M = 100), and the dotted lines denote the standard deviation (SD =15).

Distribution of Sample Across Clusters and Diagnostic Label

a)



b)

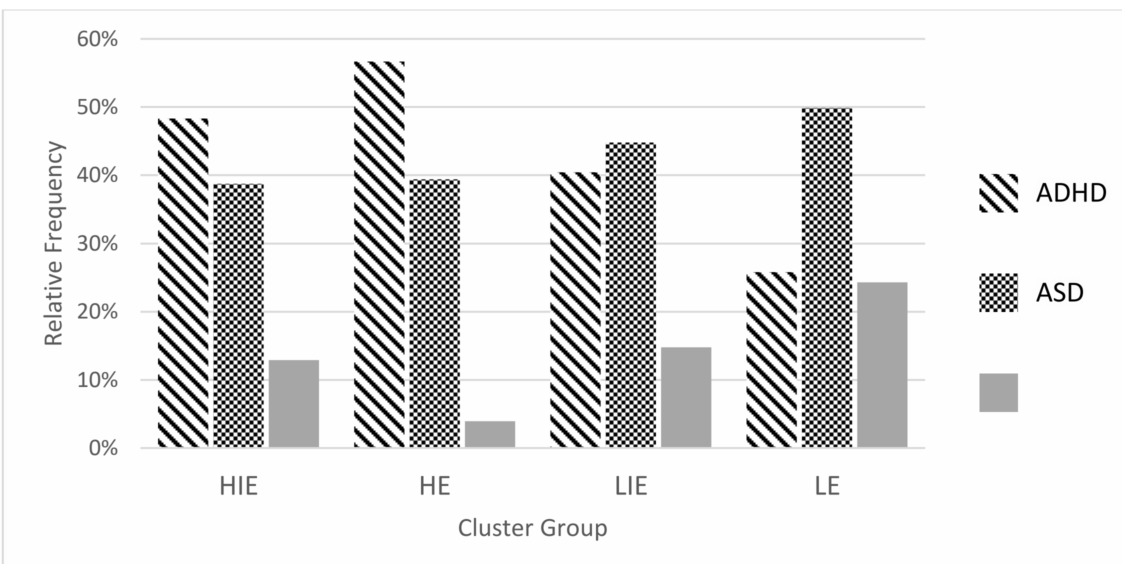


Figure 8: Distribution of clusters across primary diagnostic labels (a) is compared to the distribution of diagnostic labels across clusters (b). Derived groups and diagnostic groups significantly overlap; therefore, they are not capturing similar characteristics across the sample.

Diagnostic Group Scores on CBCL Subscale Domains

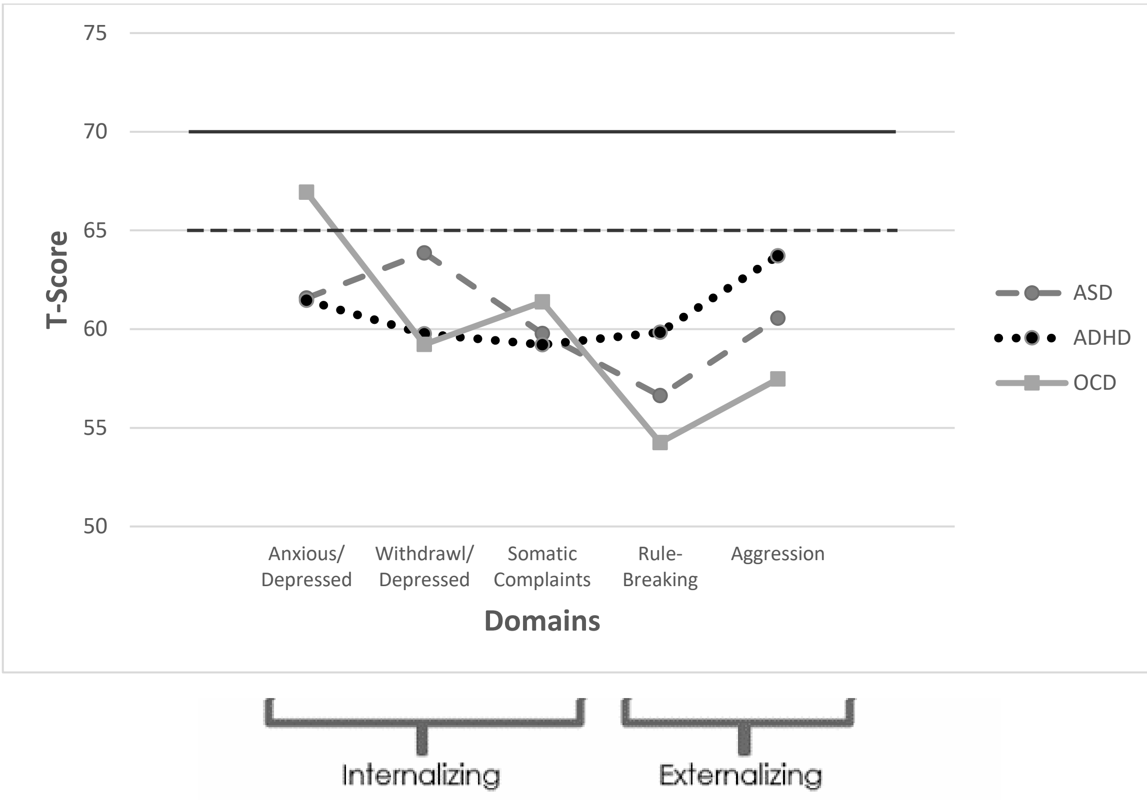


Figure 9: Mean scores on the Internalizing and Externalizing Child Behaviour Checklist (CBCL) subscales by diagnostic group (ASD, ADHD, and OCD). The solid line indicates a score above clinical range, anything between the solid and dotted line indicates borderline clinical range, and anything underneath the dotted line is outside of the clinical range. On average, diagnostic groups score below the borderline clinical threshold, and show no behavioural patterns across Internalizing and Externalizing subscales.

Behavioural Profiles of Derived Clusters

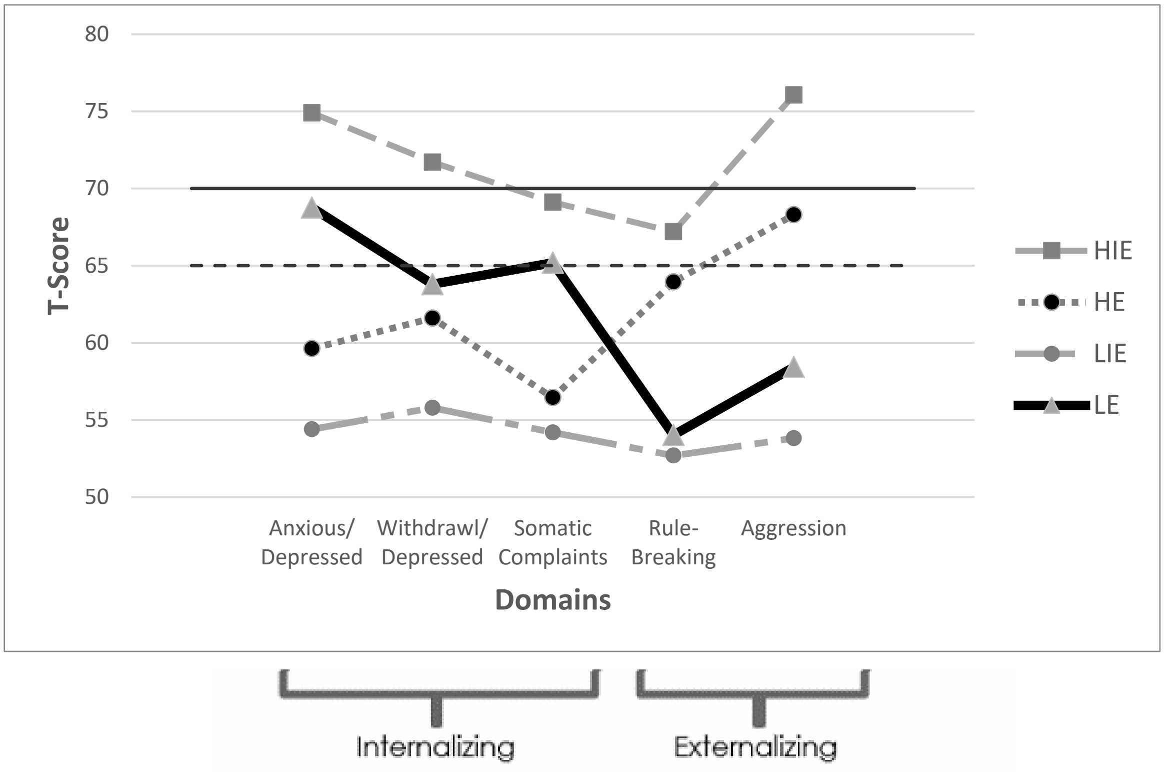


Figure 10: The mean scores on the Internalizing and Externalizing Child Behaviour Checklist (CBCL) subscales are compared across empirically derived clusters. Four behavioural profiles are identified, namely High Internalizing- Externalizing (HIE), High Internalizing (HI), Low Externalizing-Externalizing (LIE), and Low Externalizing (LE). The solid line indicates a score above clinical range, anything between the solid and dotted line indicates borderline clinical range, and anything underneath the dotted line is outside of the clinical range.

Appendices

Linear Regression Analyses

Diagnostic Labels Predict CBCL Total Score and Subscale Scores

a)

CBCL Total Scores

MIN	MEDIAN	MAX		
-35.437	0.737	32.563		
Coefficients:				
	Estimate	Std. Error	t-value	PR (>|t|)
(Intercept)	64.4374	0.3567	180.66	<2e-16***
ASD	-0.1747	0.3567	-0.352	0.725
OCD	-4.1055	0.4967	-5.885	4.86e-09***
Sig. Codes:	0 '***'	0.001 '**'	0.05 '*'	0.1 ' '
Residual Standard Error: 9.073 on 1562 degrees of freedom				
Multiple R-squared: 0.02401,			Adj. R-squared: 0.02276	
F-statistic: 19.21 on 2 and 1562 DF,			p-value 5.735e-09	

b)

Internalizing Subscale Scores (T-Scores)

MIN	MEDIAN	MAX		
-57.031	1.567	28.567		
Coefficients:				
	Estimate	Std. Error	t-value	PR (>|t|)
(Intercept)	60.4328	0.4122	146.628	<2e-16***
ASD	2.068	0.5739	3.603	0.000324***
OCD	3.5978	0.8061	4.463	4.86e-09***
Sig. Codes:	0 '***'	0.001 '**'	0.05 '*'	0.1 ' '
Residual Standard Error: 10.48 on 1562 degrees of freedom				
Multiple R-squared: 0.01537			Adj. R-squared: 0.01411	
F-statistic: 12.19 on 2 & 1562 DF			p-value:	5.58E-06

c)

Externalizing Subscale Scores (T-Scores)

MIN	MEDIAN	MAX		
-28.2921	0.3759	29.3759		
Coefficients:				
	Estimate	Std. Error	t-value	PR (>|t|)
(Intercept)	61.2921	0.4211	145.549	<2e-16***
ASD	-3.668	0.5864	-6.255	5.11e-10***
OCD	-8.3314	0.8236	-10.116	<2e-16***
Sig. Codes:	0 '***'	0.001 '**'	0.05 '*'	0.1 ' '
Residual Standard Error: 10.71 on 1562 degrees of freedom				
Multiple R-squared: 0.06567			Adj. R-squared: 0.06447	
F-statistic: 54.89 on 2 & 1562 DF			p-value:	< 2.2e-16

Suppl. Table 1: Linear Regression analyses illustrate that diagnostic labels are not accounting for much of the variation between diagnostic label and Child Behavioural Checklist (CBCL) total and subscale scores, only accounting for 2% of CBCL total scores (a), 1% of Internalizing subscale scores (b), and 6% of Externalizing subscale scores (c)

Diagnostic Labels Predict CBCL Domain Scores

	Anxiety/ Depress.	Withdrawal/ Depress.	Somatic Complaint	Social	Thought	Attention	Rule Breaking	Aggression
(Intercept)	61.509***	59.785***	59.224***	61.951***	63.215***	69.318***	59.864***	63.745***
	(0.392)	(0.354)	(0.345)	(0.349)	(0.345)	(0.400)	(0.291)	(0.391)
ASD	0.008	4.076***	0.487	2.150***	4.327***	-1.776**	-3.224***	-3.127***
	(0.546)	(0.492)	(0.481)	(0.486)	(0.481)	(0.557)	(0.405)	(0.544)
OCD	5.426***	-0.571	2.160**	-4.737***	4.942***	-10.235***	-5.615***	-6.278***
	(0.766)	(0.691)	(0.675)	(0.683)	(0.675)	(0.782)	(0.568	(0.764
R-squared:	0.036	0.052	0.007	0.063	0.060	0.100	0.01	0.046
Significance:		**** = p < 0.001;		** = p < 0.01;		* = p < 0.05		

Suppl. Table 2: Linear Regression analyses show little to no association between diagnostic labels and Child Behaviour Checklist (CBCL) domain scores. Diagnostic labels cannot account for more than 10% of the variability in domain scores, scoring highest in excluded domains.

Linear Regression Model Analyses reveal that total, and subscale scores on the Child Behaviour Checklist (CBCL) cannot be explained or predicted by primary diagnostic labels. When analyzing the predictive ability of diagnostic labels on CBCL total scores, linear regression analyses revealed a significant difference between ADHD and OCD total scores ($p = 4.86e-09$), but not between ADHD and ASD ($p= 0.725$). Overall, a significant regression equation was found ($F(2, 1562) = 19.21$, $p = 5.735e-09$), with an Adjusted R-squared value of 0.02276. This means that primary diagnostic labels could only account for 2% of the variability found in CBCL total score, making it an unreliable predictor.

When determining if diagnostic labels could predict CBCL Internalizing subscale scores, a significant regression equation was found ($F(2, 1562) = 12.19$, $p = 5.581e-08$), with an Adjusted R-squared value of 0.01411. This, however, means that diagnostic labels could only account for 1% of the variability in Internalizing subscale scores. This model suggests a significant difference between ADHD and ASD total scores ($p = 0.000324$), and ADHD and OCD ($p= 8.65e-06$).

A linear regression was calculated to predict CBCL Externalizing subscale scores based on primary diagnostic label. This model reveals a significant difference between ADHD and ASD total scores ($p = 5.11e-10$), and ADHD and OCD ($p= 2e-16$). A significant regression equation was found ($F(2, 1562)= 54.89$, $p < 2.2e-12$), with an R squared value of 0.06447. Therefore, 6% of the Externalizing subscale domains could be accounted for by diagnostic labels, which is much higher than the Internalizing and Total

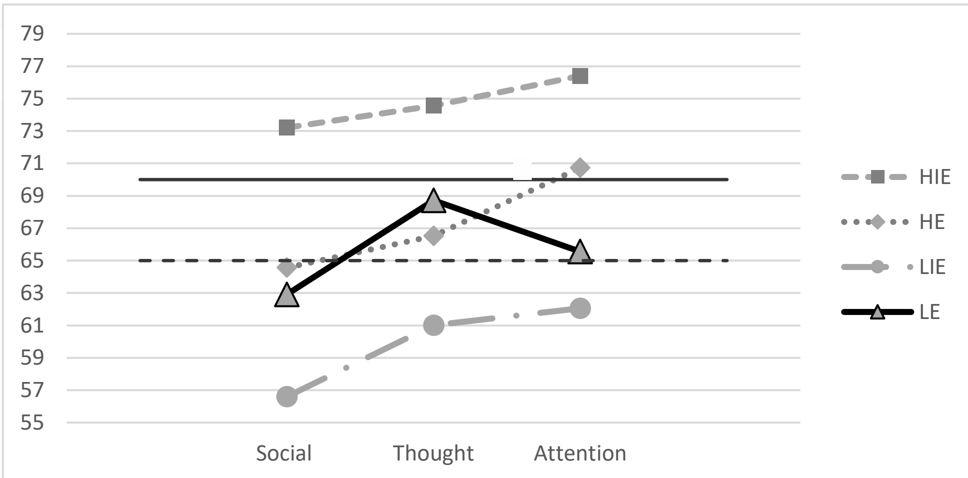
CBCL score R-square values, however, is not significant enough to make an accurate prediction.

Suppl. Table 2 reveals that Internalizing subscale domains (domain 1, 2 and 3), are not better predicted by diagnostic label when accounted for individually, (R- squared = 0.036, 0.052, 0.007, respectively). Similar findings are found in Externalizing subscale domains (domain 7 and 8), R-squared = 0.071, 0.046). Excluded domains (domain 4, 5, and 6) are explained by diagnostic labels more than subscale domains, however only less than 10% (R-squared = 0.063, 0.060, 0.100, respectively). Therefore, diagnostic labels are not reliable predictors of CBCL domain, total and subscale scores.

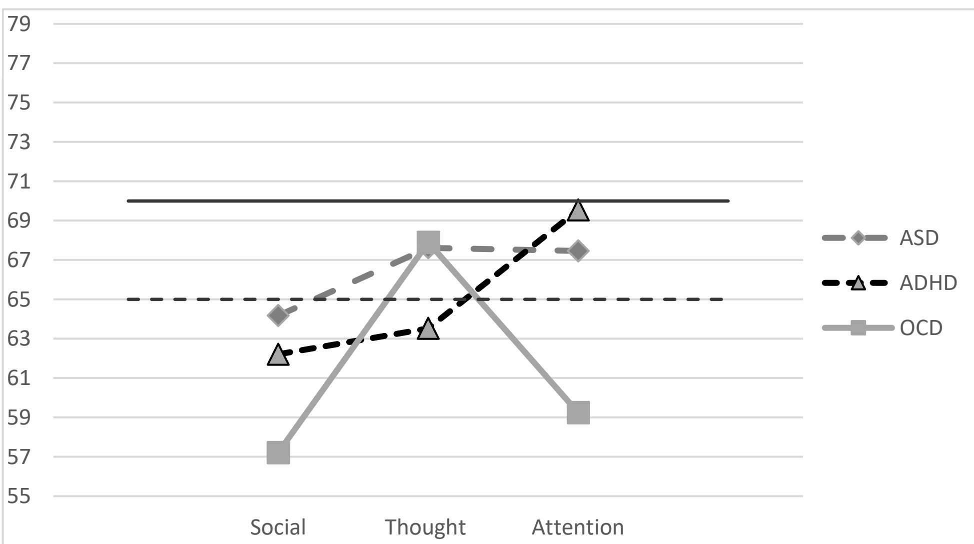
Excluded Domains

CBCL Excluded Domain Scores across Empirical Clusters and Diagnostic Labels

a)



b)



Suppl. Figure 1. Means scores of excluded Child Behaviour Checklist (CBCL) domains were compared across derived groups (a) and diagnostic groups (b). The solid line indicates a score above clinical range, anything between the solid and dotted line indicates borderline clinical range, and anything underneath the dotted line is outside of the clinical range.

Upon the suggestion of the CBCL manual, internalizing and externalizing domains were best captured when excluding the Attention problems, Social problems, and Though problem domains (Achenbach & Rescorla, 2001). These three domains also overlap with the diagnostic characteristics of ASD, ADHD, and OCD; an example of this is seen in *Suppl. Table 2*, which illustrates that diagnostic labels can account more variability in excluded domains than subscale domains. For exploratory purposes, the excluded domains were compared across primary diagnostic labels and derived labels. The following results confirm that the decision to remove the excluded domains was necessary, as no significant results were found.

The results of *Suppl. Figure 1a* illustrate that amongst the derived clusters, HIE and LIE group are still distinguishable, however the LE and HE groups are not. *Suppl. Figure 1b,* reveals that each diagnostic group is captured by one of the excluded domains. The ASD group shows borderline clinical ranges across all three domains, scoring highest on social problems. ADHD scores near clinical range in thought problems, however non-clinical range in social and thought problems. OCD shows borderline clinical range scores in Thought problems, and much lower scores in social and attention problems. This confirms that including these three domains does not benefit clinical profiles because these three characteristics are already being captured by diagnostic criteria (Achenbach & Rescorla, 2001).