Exploring the Interaction of Brain Functional Network with Cognition, Emotion, Behavior and Environment Based on Community Data

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Abstract

The current categorical psychiatric diagnosis system, which relies on superficial signs and symptoms, has been criticized for high comorbidity and heterogeneity within diagnoses, leading to questions about its reliability and validity. Many researchers are working on integrating psychopathology with neuroscience, genetics, and cognitive science to construct a new framework of psychiatric classification or propel dimensional approaches to replace categorical classification methods. Neuroscience is playing an increasingly prominent role in the development of psychology and psychopathology, especially in the demand for seeking a dimensional research methodology for transdiagnostic studies. Besides, community-based data, reflecting the natural distribution of mental illnesses, is crucial for conducting a dimensional study aimed at exploring the latent brain-behavior relation across psychiatric disorders. Studies across different psychiatric disorders have indicated that the syndromes share some physiological mechanisms in common as their basis. On the other hand, an increasing number of studies have suggested that the development of individual behavior is shaped not only by brain and genes, but also by environmental factors such as childhood socio-economic status and parenting styles. The influence of brain-environment interactions on the growth of youth may provide guidance for our parenting strategies.

A multivariate statistical method (partial least squares regression) was applied to seek associated latent pattern pairs from the whole brain resting-state functional connectivities and comprehensive phenotypic measures including behavioral, cognition and emotional assessments in a community-based sample of 699 subjects. Five psychiatric disorder groups and a healthy group were selected from those 699 subjects, and multiple group comparisons between disease and healthy groups were employed to help interpret the latent pattern pairs identified in the previous regression. In addition, a moderation model was introduced to test the moderating effect of a certain environmental factor on the relation between the identified latent brain and phenotypic pattern. A set of 23 environmental scores including measurements of social status, parental stress, parenting style, and trauma were tested in turn as moderators.

Four significant associated latent pattern pairs reflecting general behavioral problems, cognitive and language skills, externalizing problems, and social dysfunction were captured in our study. Each pair of latent patterns exhibited reasonable variations across different diagnostic groups.

Though distinct from each other, all four latent brain activity patterns involved somatomotor network on their most important connectivities. Furthermore, many environmental factors were adjudged to moderate the brain-behavior relations in certain mental illness group, most of which are about parental stress and parenting styles.

Our study dissociated four unique but overlapping latent pattern pairs across psychiatric diagnoses, providing brain functional evidence for the development of dimensional psychiatric classification system, as well as aiding our understanding of brain-behavior pathway. Additionally, moderating effects of environmental factors detected in our research suggest that a relaxed and intimate family and parental warmth are able to give children a better phenotypic outcome.

Résumé

Le système actuel de diagnostic psychiatrique catégorique, qui repose sur des signes et symptômes superficiels, a été critiqué pour sa forte comorbidité et son hétérogénéité dans les diagnostics, ce qui soulève des questions sur sa fiabilité et sa validité. De nombreux chercheurs travaillent sur l'intégration de la psychopathologie aux neurosciences, à la génétique et aux sciences cognitives pour construire un nouveau cadre de classification psychiatrique ou propulser des approches dimensionnelles pour remplacer les méthodes de classification catégorielles. Les neurosciences jouent un rôle de plus en plus important dans le développement de la psychologie et de la psychopathologie, en particulier dans la demande de recherche d'une méthodologie de recherche dimensionnelle pour les études transdiagnostiques. Des études sur différents troubles psychiatriques ont indiqué que les syndromes partagent certains mécanismes physiologiques en commun comme base. Les données communautaires, reflétant la distribution naturelle des maladies mentales, sont cruciales pour mener une étude dimensionnelle visant à explorer la relation latente cerveau-comportement à travers les troubles psychiatriques. En outre, un nombre croissant d'études ont suggéré que les comportements humains sont façonnés non seulement par les gènes, mais également par des facteurs environnementaux tels que le statut socio-économique de l'enfance et les styles parentaux. L'influence des interactions cerveau-environnement sur la croissance des jeunes peut guider nos stratégies parentales.

Une méthode statistique multivariée (régression des moindres carrés partiels) a été appliquée pour rechercher des paires de modèles latents associés à partir de l'ensemble des connectivités fonctionnelles à l'état de repos du cerveau et des mesures phénotypiques complètes, y compris des évaluations comportementales, cognitives et émotionnelles dans un échantillon communautaire de 699 sujets. Cinq groupes de troubles psychiatriques et un groupe sain ont été sélectionnés parmi ces 699 sujets, et des comparaisons de groupes multiples entre les groupes malades et sains ont été utilisées pour aider à interpréter les paires de schémas latents identifiées dans la régression précédente. De plus, un modèle de modération a été introduit pour tester l'effet modérateur d'un certain facteur environnemental sur la relation entre le cerveau latent identifié et le modèle phénotypique. Un ensemble de 26 scores environnementaux comprenant des mesures du statut social, du stress parental, du style parental et des traumatismes ont été testés tour à tour en tant que modérateurs.

Quatre paires de modèles latents associés significatifs reflétant des problèmes de comportement généraux, des compétences cognitives et linguistiques, des problèmes d'extériorisation et un dysfonctionnement social ont été capturés dans notre étude. Chaque paire de modèles latents présentait des variations raisonnables entre différents groupes de diagnostic. Bien que distincts les uns des autres, les quatre modèles d'activité cérébrale latente impliquaient un réseau somatomoteur sur leurs connectivités les plus importantes. En outre, de nombreux facteurs environnementaux ont été jugés pour modérer les relations cerveau-comportement dans certains groupes de maladies mentales, dont la plupart concernent le stress parental et les styles parentaux.

Notre étude a dissocié quatre paires de modèles latents uniques mais qui se chevauchent à travers les diagnostics psychiatriques, fournissant des preuves fonctionnelles cérébrales pour le développement d'un système de classification psychiatrique dimensionnelle, ainsi qu'une aide à notre compréhension de la voie du comportement cérébral. De plus, les effets modérateurs des facteurs environnementaux détectés dans notre recherche suggèrent qu'une famille et une chaleur parentale détendue et intime sont capables de donner aux enfants un meilleur résultat phénotypique.

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Contribution of Authors

The work presented in this thesis is not my own achievement, but the result of the collective efforts of many people, especially my master supervisors, Dr. Xiaoqian Chai and Dr. Xujun Duan. Listed below are their specific contributions:

Xiaoqian Chai: Supported the formation and evolution of the main research idea, helped with the methodology design and adjustment, helped with application for data access, provided advice on the result interpretation and discussion, and helped with writing the thesis.

Xujun Duan: Conceptualized the main research process, designed the methodology and helped with its adjustment, assisted in the interpretation and discussion of results, and provided advice on manuscripts writing.

It is also of great importance to give credit to other co-authors for their efforts. Listed below are their specific contributions (in alphabetical order):

Jinming Xiao: Assisted in the research design and method implementation (statistical analysis part), helped with result presentation, and helped with quality control of MRI data.

Xiaolong Shan: Helped with preprocessing and quality control of MRI data.

Xinyue Huang: Provided advice on result interpretation, and assisted in quality control of MRI data.

Figures and Tables

Abbreviations

ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorders
BD	bipolar disorder
BOLD	blood-oxygen-level dependent
CBF	cerebral blood flow
CBIC	CitiGroup Cornell Brain Imaging Center
CBV	cerebral blood volume
CSF	cerebrospinal fluid
CT	computed tomography
CUNY	CUNY Advanced Science Research Center
DAN	dorsal attention network
DLD	developmental language disorder
DMDD	disruptive mood dysregulation disorder
DMN	default mode network
DPABI	Data Processing and Analysis of Brain Imaging
DSM	Diagnostic and Statistical Manual of Mental Disorders
FC	functional connectivity
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
FND	functional neurological symptom disorder
FPN	fronto-parietal network
GAD	generalized anxiety disorder
GM	gray matter
HBN	Healthy Brain Network
HC	healthy control
HCP	Human Connectome Project
ICD	International Statistical Classification of Diseases and Related Health Problems
INU	intensity non-uniformity

LIM	limbic network
LPP	latent pattern pair
MDD	major depressive disorder
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
NMR	nuclear magnetic resonance
PET	positron emission tomography
PLS	partial least squares
PTSD	post-traumatic stress disorder
RDoC	Research Domain Criteria
ROI	region of interests
RU	Rutgers University Brain Imaging Center
sCCA	sparse canonical correlation analysis
SMN	somatomotor network
sMRI	structural magnetic resonance imaging
T1w	T1-weighted
VAN	ventral attention network
VBM	voxel-based morphometry
VN	visual network
WHO	World Health Organization
WM	white matter

1 Introduction

1.1 Neural Basis Across Psychiatric Diagnoses

A psychiatric diagnosis is generally a collection of some specific psychological behaviors and symptoms of the person. It relies predominantly on statements of an individual's subjective experience or descriptions of the individual's signs/behavior[1]. Psychiatric disorders, also referred to as mental illnesses, are normally divided into many different categories according to systems like DSM-5[2]. The system covers the most common or influential psychiatric disorders, including neurodevelopmental disorders like ADHD, ASD, and learning disorders, schizophrenia spectrum disorders, bipolar disorders, depressive disorders like MDD, anxiety disorders like GAD and social anxiety disorder, and disruptive, impulse-control and conduct disorders. The prevailing diagnosis criteria and treatment methods of these disorders are also based on these categorical systems.

However, categorical psychiatric diagnosis system has been increasingly criticized for focusing only on superficial signs and symptoms[3] and ignoring phenotypic problems under the diagnostic threshold, leading to questions about its reliability and validity. In addition, High degree of comorbidity is found to be widespread among disorders in categorical models like DSM-5. Due to the general lack of consensus regarding the pathophysiological comprehension of psychiatric disorders, current categorical diagnosis systems not only lead to issues in the assessments of comorbidities[4], but also obscure possible common neurological causes underlying across different disorders. Such problems in diagnosis are affecting many important areas including treatment and research. For example, the underdiagnosis of comorbidities can negatively impact their treatment outcomes[5].

In response, many researchers have turned to work on integrating psychopathology with neuroscience, genetics, and cognitive science. Some of the studies are supported by the Research Domain Criteria (RDoC) project developed by the National Institute of Mental Health, including studies that construct a new framework of psychiatric classification[6] or propel dimensional approaches to replace categorical classification methods[7]. Though fabulous in theory, such a dimensional research classification system for psychiatric disorders is very tough to build and verify thoroughly in practice. Because the diversity of clinical psychiatric symptoms and the complex brain systems involved in mental illness are difficult to be fully captured and interpreted.

Besides, studies across different psychiatric disorders, such as investigating their genetic

relationship[8], and identifying their overlapping neurostructural substrate abnormalities[9, 10] and neurofunctional disruptions[11, 12, 13], have indicated that the syndromes share some physiological mechanisms in common as their basis. Some of these studies have identified dissociable features or mechanisms associated with specific dimensions of psychiatric phenotype[14, 15, 16]. In summary, neuroscience is playing an increasingly prominent role within the development of psychology[17] and psychopathology[7, 18], especially in the demand for seeking a dimensional research methodology for transdiagnostic studies.

1.2 Community-based Data

Many researchers have linked psychiatric disorders or their symptoms to brain activities, and discovered some substantive relations. However, most of these studies have focused on clinical symptoms, but may be ignoring the intricate association between psychopathology, cognitive processes, and personality traits[19]. A comprehensive consideration of multifaceted phenotype measures across mental illnesses and health may be a vital foundation for exploring the latent association between brain activities and one's emotion, cognition, and behavior. Some psychiatric studies have introduced community-based data to explore the continuities across disorders and avoid bias[20, 21]. Besides, community-based data can provide more informative input to data-driven approaches to produce more referential results[22].

1.3 Resting-state Functional MRI

Resting-state functional magnetic resonance imaging is widely used to measure intrinsically organized patterns of spontaneous signal fluctuations in BOLD signal[23]. The data is commonly referred to as resting-state functional connectivity, the statistical dependence between time series of BOLD signals in distinct regions of the brain[24], which is also considered to be associated with structural connectivity[25, 26].

Extensive phenotypes derive from coordinated interactions throughout the entire brian connectome[27, 28], thus checking the whole-brain connectivity without prior assumptions is essential for our study. Besides, many functional brain imaging studies were focusing on higher-order association networks[29, 30], some have found the networks related with certain clinical symptoms[30, 31].

So it is also of great importance to pay attention to the connectivity within and between large-scale brain networks.

1.4 Development Shaped by Genetic and Environmental Factors

The great nature or nurture debate on brain development has been discussed for years, leading to a widely acknowledged consensus that neural circuits and behavior are co-shaped by genes and environment[32]. Although the effects of genes on the construction of complex brain network architecture have long been depicted and accepted, the influences from environment was hugely ignored. In addiction to the relatively straightforward impact of visual environment on the shaping of visual cortex[33], some intangible environmental factors, such as parenting[34], social environment[35], and childhood socio-economic status[36], have been more and more emphasized for their influences on the brain development. Besides, some studies have linked the influence from certain factors with specific brain functional networks[37], suggesting that influences of an environmental factor on development may manifest in specific functions.

In addition to influencing one's behavioral performance by shaping the development of the brain, many studies have also found that environmental factors can change the phenotypic outcomes by affecting the relationship between brain and behavior[38, 39]. On the one hand, some studies have revealed that certain environmental factors have varying degrees of influence on individuals with mental illness[40, 41], while the behavior of healthy individuals is relatively stable. On the other hand, some environmental factors were found to have a significant impact on behavioral performance of healthy individuals, but hard to change the related symptoms in patients with psychiatric disorders. For example, according to the research [42], aspects of the family environment like family expressiveness, cohesion, and organization can influence the development of executive functions in children without ADHD, but not affect those functions in children diagnosed with ADHD. According to these findings, the influence of environmental factors on individual final behavior is relatively flexible. Considering that executive dysfunction is a major deficit of ADHD[43], these studies also suggest that the impact of environment in a certain behavioral dimension depends on one's strength of the brain-behavior relationship in this dimension, and brain-behavior relationships varies in different psychiatric disorders.

2 Background

2.1 Psychiatric Disorders in Categories

Due to the complexity of their causes and the difficulty of treatment, psychiatric disorders have always been one of the biggest problems that plague mankind. Current psychiatric diagnostic schemes are based on categorical psychiatric diagnosis systems such as the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[2]. According to the statistics of the World Health Organization (WHO), currently known mental illnesses can be divided into 10 major categories and 72 subcategories, with a total of more than 400 kinds. Besides, about one in eight people in the world suffers from at least one mental illness, and the proportion is increasing rapidly. Among all these psychiatric categories, emotional disorders such as anxiety disorders, depressive disorders and bipolar disorder (BD) have the highest prevalence[44], while neurodevelopmental disorders like attention deficit hyperactivity disorder (ADHD) and autism are also considered to have a relatively high incidence[45]. A former study have conducted statistical analysis on the negative impact of mental illness in China, and found that the burden of disease caused by mental disorders accounts for as high as 13% of all non-communicable diseases[46]. Its increasing incidence and the huge burden it brings to patients and their families have made psychiatry-related theoretical and clinical research become an important global issue.

Neurodevelopmental Disorders

The development of the nervous system is a finely regulated and time-bound process influenced by both genetic programs and the environment. Early in life, any significant deviation from normal developmental trajectories can lead to missing or abnormal neuronal structure or connectivity[47]. Because of the temporal and spatial complexity of brain development, many potential triggers of neurodevelopmental disorders may affect different regions of the nervous system at different times and ages. These factors consist of internal factors like genes, metabolic diseases, immune disorders, infectious diseases, nutritional factors and physical trauma, as well as external environmental factors such as social deprivation.

Neurodevelopmental disorders are a group of psychiatric diseases that affect the development of the nervous system. The disturbed development of the patients will lead to abnormal brain function,

which may eventually affect their emotional regulation, learning ability, self-control, social ability, memory, and other aspects of behavioral activities[48]. The effects of neurodevelopmental disorders are often lifelong. According to DSM-5, neurodevelopmental disorders mainly include ADHD, autism spectrum disorder (ASD), developmental language disorder (DLD), motor disorders, and specific learning disorders. Some neurodevelopmental disorders, such as ASD, are considered to be neurodevelopmental syndromes caused by the convergence of many factors[49]. Although many overlapping on behavior have been found between different subdivisions of neurodevelopmental disorders[50, 51], the diagnosis of related diseases is still based on the patient's explicit behavioral symptoms.

The main symptoms of ADHD are characterized by attention deficit, hyperactivity and impulsiveness. Studies have shown that symptoms of ADHD are mainly caused by impaired executive function[52, 53], and low control over emotions is considered to be its core symptom [54, 55]. For children with ADHD, their attention deficits may lead to poor academic performance, impair their normal cognitive and social function development, and have serious adverse effects on their family and peer relationships[56]. As for adult ADHD patients, they can usually develop their own skills to hide hyperactivity symptoms and make them similar to healthy individuals on external behaviors, but more inner anxiety would be suffered. Besides, ADHD patients are prone to comorbidity with other emotional disorders, which leads to further deterioration of their health[57]. Although the negative impact of ADHD is enormous, its causes remain unclear. Many studies have proved that genetic factors play an important role in its pathogenesis[58], ADHD is often inherited in families, and the heritability is up to 74%[59], while others found mothers' exposure to toxins, infections or brain damage during pregnancy a key factor in triggering ADHD[60]. On the other hand, there is no universal guideline for the treatment of ADHD, different countries and institutions are recommending different strategies including pharmacotherapy and behavioral interventions[61, 62]. Overall, the debate over the diagnosis and treatment schemes for ADHD has been going on for years[63], and there is still a great need for research on the psychopathology and therapy of ADHD.

ASD, also referred to as autism, consists of a group of neurodevelopmental disorders that share common features including deficits in social interaction and communication, limited range of interests, and repetitive stereotyped behaviors[64]. As a spectrum disorder, ASD exhibits complicated heterogeneity among patients, making it hard to reach a consensus on its specific impaired neural

circuits. Controversy over its diagnostic criteria and phenotype range still persists today[65]. The causes and treatment strategies of ASD are also in the exploration stage. Both genetic[66, 67] and environmental factors[68] are reported to be associated with its onset.

Emotional Disorders

Emotional disorders, such as anxiety and depressive disorders, are a group of chronic psychiatric disorders involving abnormal emotion regulating function, which have been largely linked with impaired quality of life, and interpersonal functioning[69]. These diseases can emerge in childhood or young adolescence, and have a high probability of recurrence, which means that their detrimental effects can be sustained throughout the lifespan.

The anxiety emotion of patients with anxiety disorders cannot subside naturally, but may aggravate over time. Such symptoms will seriously interfere with their normal work and life[70]. According to the definition in DSM-5, there are several specific types of anxiety disorders such as generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder. Patients with GAD usually have persistent anxiety or panic, tend to be nervous or irritable, while patients with social anxiety show more fear of communicating with others or even making eye contact[2]. According to a study [71] in 2010, anxiety disorders have the highest prevalence rate in mental illnesses, among which social anxiety disorder alone has a prevalence rate of 10%. Besides, there is strong heterogeneity in GAD and panic disorder, all these features make anxiety disorders one of the most significant psychiatric issues today. However, there are no objective biomarkers available for the diagnosis of anxiety disorders, and their clinical diagnoses often rely on a series of questionnaires measuring patients' phenotypes[72]. On the other hand, although some environmental risk factors for anxiety disorders have been discovered[73], and some behavioral therapies have been reported to improve anxiety symptoms in some patients[74, 75], the underlying mechanisms remains unclear.

Depressive disorders are a group of psychiatric disorders defined in DSM-5, including disruptive mood dysregulation disorder (DMDD), major depressive disorder (MDD) and persistent depressive disorder[2]. Depressive disorders are characterized by severe or persistent sadness that interferes with normal life, and patients show reduced interest in or enjoyment of activities. Considering its high morbidity rate that continues to rise, the burden on the global economy and society of depressive disorders may be far beyond our expectations[76, 77]. As for its pathology, it is generally

accepted that physical, psychological, and social factors all play prominent roles in the development of depressive disorders[78]. A diathesis-stress hypothesis about the causes of depression pointed out that the vulnerability of human may come from genetic inheritance, while postnatal stressful events may lead to depressive disorders in relatively vulnerable individuals[79]. In addition, current treatment methods for depressive disorders involve multiple aspects like psychotherapy and pharmacotherapy, and specific therapy plan generally needs to be adjusted according to the patient's symptoms, resistance, and personal preferences[80].

2.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a medical imaging technology that utilizes strong magnetic fields, magnetic field gradients and radio waves to accurately image tissues in the human body. MRI is a non-invasive technology, and unlike computed tomography (CT) and positron emission tomography (PET), MRI does not involve the use of ionizing radiation. The invention of MRI originated from the discovery of nuclear magnetic resonance (NMR). NMR was first described and measured in 1938 by the Stern-Gerlach experiment [81], and then demonstrated in condensed matters by Felix Bloch and Edward Purcell[82]. It is a physical phenomenon describing that the atomic nucleus will change from randomly oriented spins to ordered spins in an externally applied constant strong magnetic field. When a radio frequency (same as the precession frequency of the spin nucleus) pulse perpendicular to the direction of the magnetic field is emitted, the nucleus will absorb the energy and jump to a higher energy excited state[83]. Relaxation is the process by which the excited state nucleus releases energy and turn back to the low-energy state. In this process, the magnetization vector recovers toward the direction of the magnetic field, which can be decomposed into two parts: longitudinal and transverse magnetic relaxation, with T1 and T2 referring to their time respectively. Based on the different relaxation times of atomic nuclei in the magnetic field, a multi-directional magnetic field gradient encoding method was invented to locate the echo signal in the magnetic field, and finally realized the imaging of nuclear magnetic resonance signals in space[84].

Structural Magnetic Resonance Imaging

T1-weighted (T1w) imaging is one of the most basic and common MRI pulse sequences, and it is mainly used to scan the brain and characterize its structure. The T1w imaging relies on the difference in T1 time of different brain tissues caused by their difference in water content. The gray matter (GM) part mainly contains neuronal cell bodies and glial cells, and has significantly higher water content and longer T1 than the white matter (WM) composed of myelinated axons. Structural magnetic resonance imaging (sMRI) can take advantage of their disparity on relaxation time to clearly delineate brain structures as gray scale on images. sMRI has many advantages such as non-invasiveness and high resolution, and is widely used in clinical assessment and diagnosis, as well as in psychopathological research. The voxel-based morphometry (VBM) method is one of the most commonly used methods for studying sMRI brain images, allowing researchers to quantify the concentration of structural tissue in different regions of the brain[85]. Besides, surface-based methods are rapidly developing, which unfold the cortex into a two-dimensional plane to avoid the influence of smoothing and other operations in three-dimensional space[86, 87].

Functional Magnetic Resonance Imaging

Structural MRI provides us with a non-invasive method to examine the anatomical structure of the brain, but it cannot capture the functional activities of the brain, and the emergence of functional magnetic resonance imaging (fMRI) provides a new perspective for revealing the cerebral activity state. Scanning process of fMRI detects time-varying signals in the brain, including blood-oxygen-level dependent (BOLD) signal, cerebral blood volume (CBV), and cerebral blood flow (CBF). The BOLD imaging technology proposed by Ogawa is currently the most popular fMRI method, which is designed for scanning living bodies, especially the brain[88]. According to a former study [89], blood flow on the cerebral cortex is coupled to the intensity of neuronal activity, as activity in parts of the brain will increase local oxygen demand. BOLD imaging technology is based on this fact, measuring neuronal activity in the brain by detecting changes in BOLD signals[90].

Resting-state fMRI is a method of fMRI, evaluating the spontaneous interaction of different regions of the brain in the absence of any external stimuli. The resting state refers to a state of relaxation in which the brain is task-free, and generally involves involuntary thought activities like

rumination of the past or planning for the future. Biswal et al. found that the brain activity of the human during rest also contains information about the functional composition of the brain network, and detected highly temporally correlated BOLD signals in the motor cortex regions on both sides of the brain[91]. Similarly, by exploring the time correlation of BOLD signals in different brain regions in the resting state, many large-scale functional networks have been discovered, and the basic division of brain functional networks has been realized[92]. In summary, resting-state fMRI provides a solid foundation for our study of the brain functional organization, and is widely used because of its applicability.

To further explore the interactions between different brain regions, functional connectivity (FC) data were proposed to represent the temporal correlation of neurophysiological events between two regions in the brain[93]. Based on the basic assumption that brain regions that undergo similar changes in time are functionally connected[94], FC data can be used to represent the relationship between different brain regions in resting or task states. The field of FC's application is also very wide, and it has been used not only in fMRI, but also in other modalities of brain activity data[93, 95], providing us with a powerful tool for the study of the functional architecture of the brain.

2.3 Transdiagnostic Psychiatric Studies

Diagnosis of mental illness began in Europe at the end of the 17th century. Influenced by animal and plant taxonomy, the categorical classification of mental illness has become an indispensable part of modern clinical practice[96]. At present, the diagnosis of mental illness mainly relies on categorical systems such as the International Statistical Classification of Diseases and Related Health Problems[97] (ICD) or DSM[98]. However, while the establishment of these diagnostic codes lays the foundation for the diagnosis and treatment of psychiatric disorders, it also brings potential subjective misdiagnosis caused by the lack of objective and quantifiable indicators, as well as the problem of comorbidity and heterogeneity[99, 100], which may further affect the treatment. In order to solve these problems, an increasing number of studies are turning their attention to trying to define basic dimensions that can span various types of mental illness, and to try to recognize individual psychiatric symptoms as different combinations of these basic dimensions, so that mental illnesses can have measurable abnormal categories in different dimensions[101].

Additionally, in order to introduce objective and quantifiable indicators in psychiatric research, the use of brain MRI data is indispensable. In recent years, more and more studies have associated it with clinical phenotypic measures of various mental diseases. Some researchers believe that the symptoms displayed by each patient with mental illness should be the result of a combination of brain circuit abnormalities in different dimensions. In a previous transdiagnostic study [31] based on brain images and psychiatric screening data of 663 youths, researchers utilized sparse canonical correlation analysis (sCCA) and found four dimensions of psychopathology, respectively reflecting psychosis, mood, fear, and externalizing behavior, and all have their distinctive corresponding brain circuits. Besides, this study also found a common feature of four brain circuit dimensions: insufficient segregation between the default mode network and the executive network. Another transdiagnostic study [19] based on MRI and phenotypic data of 110 healthy subjects, 40 BD patients, 37 ADHD patients, 29 schizophrenia patients and 8 schizoaffective disorder patients introduced a multivariate data-driven approach, and also identified three latent psychopathological dimensions representing general psychopathology, cognitive dysfunction, and impulsivity, along with three associated unique whole-brain resting-state FC patterns. In addition, altered connectivities within the somatosensory-motor network and between it and other networks were captured in all three FC patterns in this research. In another recently published study [102], the researchers also utilized MRI and behavioral measures of transdiagnostic patients to identify generalizable brain functional biomarkers for psychiatric symptoms, and dissociated three clinical domains corresponding to psychosis-positive, attention deficit and appetite-energy. These studies above have preliminarily validated the feasibility of the dimensional approach and discovered some similar psychopathological dimensions based on MRI data. Future dimensional psychiatric studies can take advantage of their conclusions to explore other key aspects of mental illness such as intervention and treatment.

2.4 Environmental Factors in Psychopathology of Children and Adolescents

According to several community-based surveys from high-income countries, between 10% and 14% of children and young adolescents could be diagnosed with a psychiatric disorder, and this rate would rise to about 25% by late adolescence and early adulthood[103]. Mental health problems in childhood and adolescence not only damage the patient's life at that time, but also may lead to

severe functional impairment in adulthood. However, about 75% of mental illnesses occur before the age of 24[104]. Since childhood and adolescence is a crucial period for mental healthy, individuals in this stage usually experience huge influences from external environmental factors, including cooperation and competition with peers, affirmation and criticism from teachers, and more importantly, family factors such as parenting style and family atmosphere. Many studies have focused on the relationship between parental and family factors and psychiatric disorders or symptoms in children and adolescents. For patients diagnosed with separation anxiety disorder in childhood, a study found that parent-child interaction therapy can significantly reduce their separation anxiety behavior, suggesting that parental factors hugely affect children's anxiety[105]. Other studies have discovered that experiencing parental divorce in childhood or adolescence is associated with the incidence of schizophrenia and BD[106], and mania, depression, and parent-rated problem behaviors of adolescent BD patients would stabilize in two years after family-focused treatment[107], reaffirming the importance of family factors in children's emotional and behavioral outcomes.

On the other hand, childhood and adolescence are critical phases of rapid neural growth and development, during which the brain is so vulnerable that the impact of environmental factors may play a decisive role in its subsequent progress. It is reported that youths from higher socioeconomic status families have lower T1w/T2w ratio in widespread cortical regions and better language related abilities[108]. Other researchers uncovered that maternal behavior in parent-child interaction is related with children's activities in brain regions involved in emotion processing[109], and a warm and supportive maternal parenting style is correlated with less amygdala activity towards fearful facial expressions in adolescents[110]. On the contrary, parental abuse and severe stressor during childhood or adolescence can lead to chronic post-traumatic stress disorder (PTSD) and other psychopathology including internalizing or emotional and externalizing or behavioral problems. Besides, a negative correlation of intracranial and cerebral brain volumes with parental abuse duration was reported, indicating that childhood maltreatment may have a global and cumulative adverse impact on brain and behavior development[111]. Another study in 2002 revealed that exposure to maternal stress in early childhood may induce elevated cortisol levels, while high preschool cortisol levels was also found to be associated with greater psychiatric symptoms in first grade[112]. In the above studies, family factors, as a very critical environmental variable in childhood and adolescence, showed global influences on children's development of brain, emotion, and behavior, but

all limited to one mental illness or a single psychiatric dimension. A more comprehensive study that includes more environmental factors and more psychiatric disorders needs to be proposed.

3 Methods and Materials

3.1 Participants

To investigate the interaction between brain and cognition, emotion, behavior and environment, we downloaded the Healthy Brain Network (HBN) dataset[113] from the Child Mind Institute's data portal. HBN project is an ongoing initiative that has been collecting data by using a community-referred recruitment model to achieve a representative epidemiologic design. We analyzed 2242 participants of ages 5-22 in total, who was involved in the deployment phase of the HBN project and had both structural and resting-state functional neuroimaging.

Before analysis, all structural images were rated from 1 to 5 by three experienced personnel. While higher score implements the image is less affected by motion artifacts, participants with average scores lower than 3 (n=1115) were excluded[114]. Figure 1 shows five representative examples of structural brain images of different scores. Besides, participants with excessive head motion (mean framewise displacement over 0.25mm) during the resting-state fMRI scan (n=329) and too few phenotypic data (n=99) were also excluded[115], led to a set of 699 participants (281 females; mean age=11.9 ± 3.4 years) for statistical analysis.

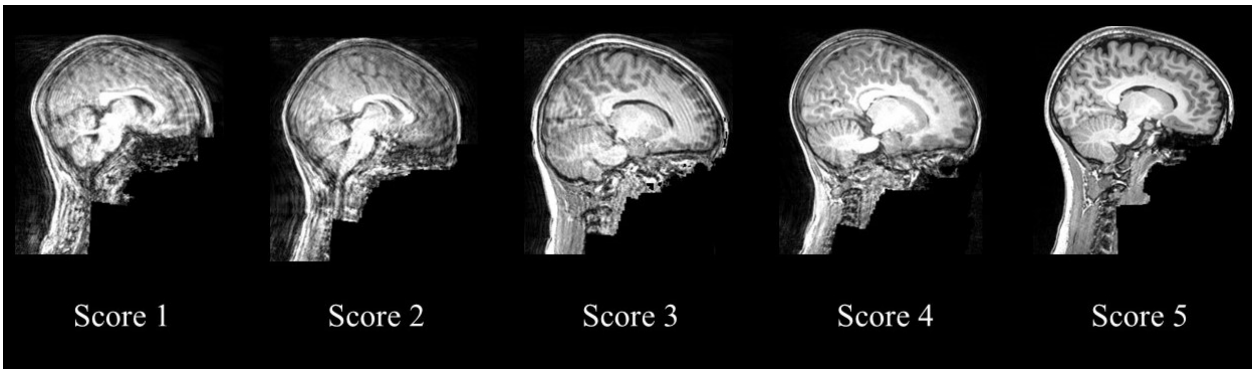

Figure 1: Typical examples of structural brain images of five different scores.

All participants underwent a series of measures according to the HBN assessment protocol. Beside, follow-up assessments for several specific psychiatric disorders were applied to participants

with a suspicion of having corresponding problems. After exclude scales that are irrelevant or with low completion rates, a set of 71 phenotypic data from 19 different measures and questionnaires were selected for the PLS analysis. These data consist of behavioral measures, cognition and language assessments, and substance use and addiction measures (Figure 2C). Besides, there were 23 environmental data for each participant, including social status, family structure, stress and trauma.

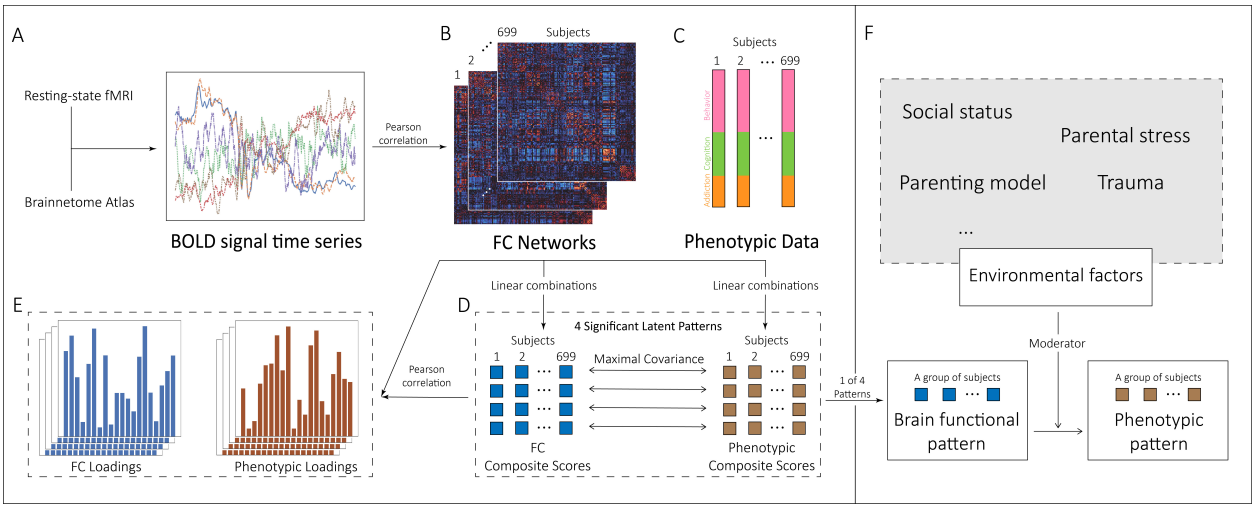

Figure 2: Schematic of the whole analysis process. **(A)** Resting-state fMRI data analysis process. After preprocessing, the 246 ROIs Brainnetome atlas were used to extract BOLD signal time series of the whole brain. **(B)** The 246×246 whole brain functional connectivity matrices for subjects in the research sample (n=699). The FC values were calculated from BOLD signal by Pearson correlation. **(C)** Phenotypic data for 699 subjects. Each subjects have a set of 71 phenotypic data including behavioral measures (marked in pink), cognition and language assessments (marked in green), and substance use and addiction measures (marked in orange). **(D)** PLS regression found 4 pairs of FC and phenotypic composite scores with maximized covariances. Each row of FC or phenotypic composite scores were linear combinations of the subjects' FC or phenotypic data. **(E)** Four groups of FC and phenotypic loadings of the latent patterns. A loading was the Pearson correlation coefficient between the original data and the composite score, representing the importance of this data for the LPP. **(F)** Moderation analysis schematic for one latent pattern pair. For a specified group, their FC composite scores of the latent pattern pair were introduced as the independent variable, while their phenotypic composite scores were introduced as the outcome. The moderating effect of 23 environmental factors, including social status, parental stress, parenting model, and trauma, were tested in turn.

Six groups of participants with different diagnostic conditions were selected from all the involved data for post PLS analysis and moderation analysis. Five groups consisted of participants diagnosed with specific psychiatric diseases or disease categories, including ADHD (n=377), ASD

(n=93), anxiety disorders (n=267), depressive disorders (n=102), and specific learning disorders (n=195). One group consisted of participants who did not receive any diagnosis (n=55). Because each participant may have been diagnosed with multiple diseases, and comorbidities are prevalent in this dataset, overlapping exists in those five diagnosed groups.

3.2 MRI Data Acquisition and Processing

The MRI data involved in this study were collected from three different HBN sites around the New York City region: Rutgers University Brain Imaging Center (RU), CitiGroup Cornell Brain Imaging Center (CBIC), and CUNY Advanced Science Research Center (CUNY). The site RU was using a 3T Siemens Tim Trio MRI scanner, while the other two sites were using 3T Siemens Prisma scanners. All three sites applied the same MRI scan parameters for both Human Connectome Project (HCP) sequence T1w images (slices=224; voxel size=0.8mm; TR=2500ms; TE=3.15ms; flip angle=8°) and fMRI images (slices=60; voxel size=2.4mm; TR=800ms; TE=30ms; flip angle=31°).

The preprocessing analysis of MRI images were performed by using a standard volumetric preprocessing pipeline of fMRIPrep v20.2.3[116], a Nipype[117] based tool. The T1w images were firstly corrected for intensity non-uniformity (INU) to be used as a anatomical T1w-reference in the following workflow. The main steps for the preprocessing of the resting-state fMRI data in fMRIPrep includes: generate a BOLD reference volume, co-register the BOLD reference to the T1w reference, estimate the head-motion parameters by comparing to the BOLD reference, correct slice-time, and resample the BOLD time-series into standard Montreal Neurological Institute (MNI) space.

To preserve any possible follow-up analysis, fMRIPrep output many derivative confounds rather than perform denoising itself. Following fMRIPrep, we implemented a 36-parameter confound regression for the resting-state fMRI images. The 36P regression model consists of 9 basic regressors including 6 motion estimates, mean signal in WM, mean signal in cerebrospinal fluid (CSF) and global signal, as well as their derivatives, quadratic terms, and squares of derivatives, and was reported to have good performance[118]. Denoised data were subsequently smoothed with a 4mm full-width at half maximum Gaussian kernel, band-pass filtered from 0.01 to 0.1 Hz, and censored by scrubbing (cut time points with Jenkinson's framewise displacement>0.2), by using

the toolbox for Data Processing and Analysis of Brain Imaging (DPABI)[119].

3.3 Functional Connectivity

To obtain the resting-state FC, each brain image was divided into 210 cortical and 36 subcortical regions of interests (ROIs) by utilizing Brainnetome atlas[120]. Functional MRI data can be extracted as blood-oxygen-level-dependent signal time series for of ROI (Figure 2A). The parcellation could be assigned to 8 resting-state networks, including 1 subcortical network and 7 on cerebral cortex[92]: visual network (VN), somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LIM), fronto-parietal network (FPN), and default mode network (DMN). Pearson correlation was computed between every pair of time series from 246 ROIs to construct a 246×246 FC matrix for each subject (Figure 2B). Such a FC matrix comprised 30135 unique connectivity values.

3.4 Partial Least Squares Regression

Partial least squares (PLS) regression is a multivariate statistical method that allows comparison between two datasets and take into account their latent patterns. Its computation maximizes the covariance between two high-dimensional variables by projecting them to new spaces. The covariance measures how two variables vary together from their mean values. Thus, the PLS is capable of detecting intricate co-variation relations between neuroimaging and phenotypic data[121]. The FC values and phenotypic measurement scores of all the subjects were organized as two input matrices of PLS regression analysis. Both matrices were linearly projected across subjects into latent patterns iteratively (Figure 2D). A latent pattern pair(LPP) consists of two corresponding latent patterns therefore represents an intrinsic relationship between two datasets that leads to the maximum covariance, and these two latent pattern should best explain each other. For every LPP, there is a fixed projection vector for connectivity data, and the FC composite score for a participant is the value of linear combination of his or her FC data using the projection vector as weights. The same process works in the phenotypic part too. After the PLS regression analysis, a 1000-time permutation test was performed, and the statistical significance was set at false discovery rate (FDR) corrected p value < 0.05.

To interpret the meaning of each phenotypic latent pattern and measure the contribution of a phenotypic measure to the LPP, the correlation coefficient was computed as the Pearson correlation between this data and the phenotypic composite score[122, 19]. The correlation coefficient values, named as loadings, represent the contribution of the original data to this LPP (Figure 2E). The loading of each brain functional connectivity was calculated by the same procedure. Both large positive and negative loadings are denoting great importance of FC data or phenotypic measures. Furthermore, a bootstrapping procedure with 500 samples constructed by resampling the phenotypic data of subjects was applied. A final Z score for each phenotypic data was obtained by dividing its correlation coefficient by its standard deviation in the bootstrapping results[19]. The Z scores were subsequently converted into p values and were FDR corrected.

3.5 Post PLS Analysis

To test whether the composite scores show differences between subjects with different diagnoses and healthy controls, several group comparisons were applied on five diagnosed groups. For each diagnosed group, we utilized a greedy algorithm to generate a age and sex matched dataset between it and the healthy control (HC) group (due to the the disproportionately low proportion of female in the ASD group, the greedy algorithm omitted matching on gender to ensure a decent sample size)[123]. Table 1 shows participants's demographic information. Kolmogorov-Smirnov tests were subsequently performed to identify whether the data is normal distributed. Both phenotypic and FC composite scores between patients and HC were then compared using two-samples T test for normally distributed data or Mann-whitney U tests for non-normally distributed data.

3.6 Moderation Analysis

Moderating effect is an interacting effect of a moderator variable who affects the relationship between a independent predictor and an outcome. To determine the moderating effect of environmental factor, a classic distinction method[124] based on linear regression analysis was applied on them along with the results of PLS regression analysis. Specifically, in a moderation model consists of a predictor (X), an outcome (Y) and a moderator (M), the relationship can be represented by the

	ASD	HC	p Value
Age (years)	12.19 (3.40)	12.19 (3.32)	1.00^a
Sex (male/female)	72/19	26/20	0.006^b
	ADHD	HC	p Value
Age (years)	11.85 (3.29)	11.85 (3.37)	1.00^a
Sex (male/female)	248/126	27/24	0.06^b
	Anxiety Disorders	HC	p Value
Age (years)	12.31 (3.35)	12.31 (3.22)	1.00^a
Sex (male/female)	146/120	26/20	0.84^b
	Depressive Disorders	HC	p Value
Age (years)	12.23 (2.71)	12.22 (2.64)	1.00^a
Sex (male/female)	52/49	16/12	0.60^b
	Learning Disorders	HC	p Value
Age (years)	14.23 (2.72)	14.22 (2.64)	1.00^a
Sex (male/female)	120/74	30/24	0.40^b

Table 1: Participants' demographic information. Standard deviations of age are in parentheses. ^{a}p Value was computed by two-samples t-test. ^{b}p Value was computed by χ^2 test.

following regression equation:

$$Y = \beta_0 + \beta_1 X + \beta_2 M + \beta_3 XM + \epsilon$$

The moderating effect of M is evaluated by estimate the parameter of the interaction term.

For each pair of latent patterns in PLS results, the FC composite score was considered as a independent predictor, while the phenotypic composite score was considered as the outcome. All 23 environmental scores were taken in turn as the moderator to test the significance of moderating effect (Figure 2F). In addition, all environmental scores and composite scores were mean-centered before regression to eliminate possible effects. Considering that the behavior of patients may be more susceptible to environmental factors, and different categories of psychiatric diseases may lead to vulnerability on different aspects, the moderation analysis were performed among the five diagnosed groups and the HC group separately. FDR corrections were then applied for the p-values of the FC-environment interaction term in each group and each latent pattern pair.

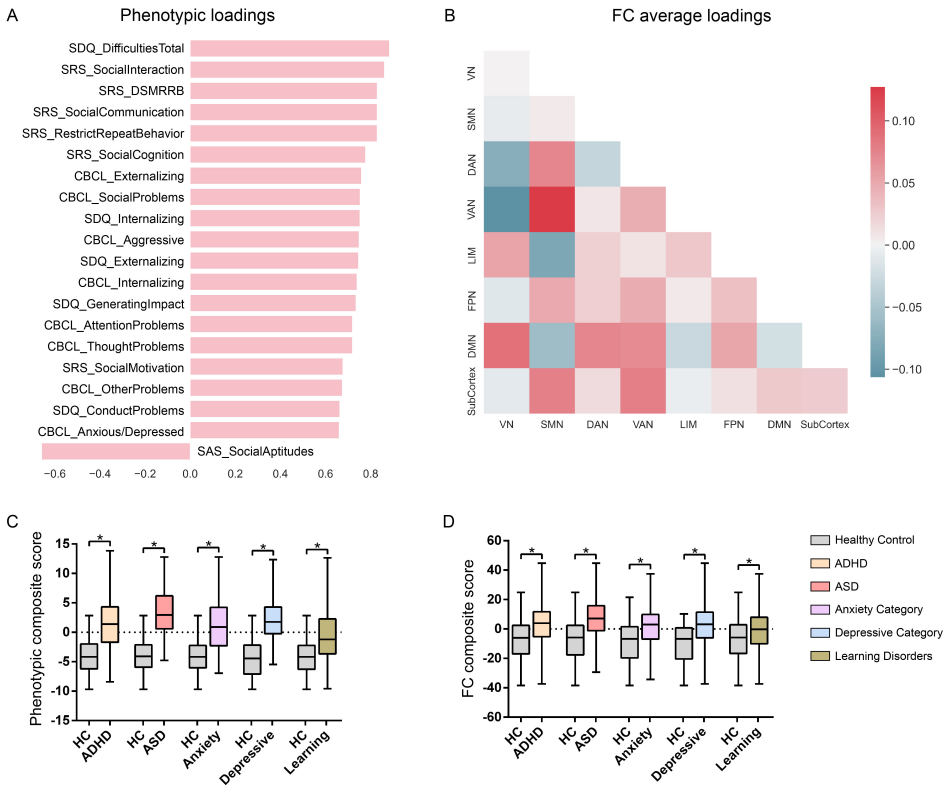

Figure 3: LPP1 - General Behavioral Problems. **(A)** Phenotypic measures with top 20 absolute values of loadings. All measures are marked in pink to denote that they are behavioral measures. Greater loading in LPP1 was associated with more severe general behavioral problems. **(B)** FC loadings averaged within and between 8 networks. The color denotes whether the greater FC is positively (in red) or negatively (in blue) associated with LPP1. **(C)** Group differences in phenotypic composite score between diseases and HC. **(D)** Group differences in FC composite score between diseases and HC. Asterisks indicate significant group difference identified by two-samples t tests or Mann-Whitney U tests ($p < 0.05$). Inset shows the color for diagnostic groups.

4 Results

4.1 Latent Patterns of Phenotype and Brain Connectivity

In the PLS regression analysis, 71 phenotypic data and 30135 FC data of 699 participants were studied. All the data were normalized across participants before regression to eliminate the effect of their original scales. The permutation test after PLS eventually suggested four pairs of significantly linked ($p < 0.05$, FDR corrected) patterns: LPP1, LPP2, LPP3, and LPP4.

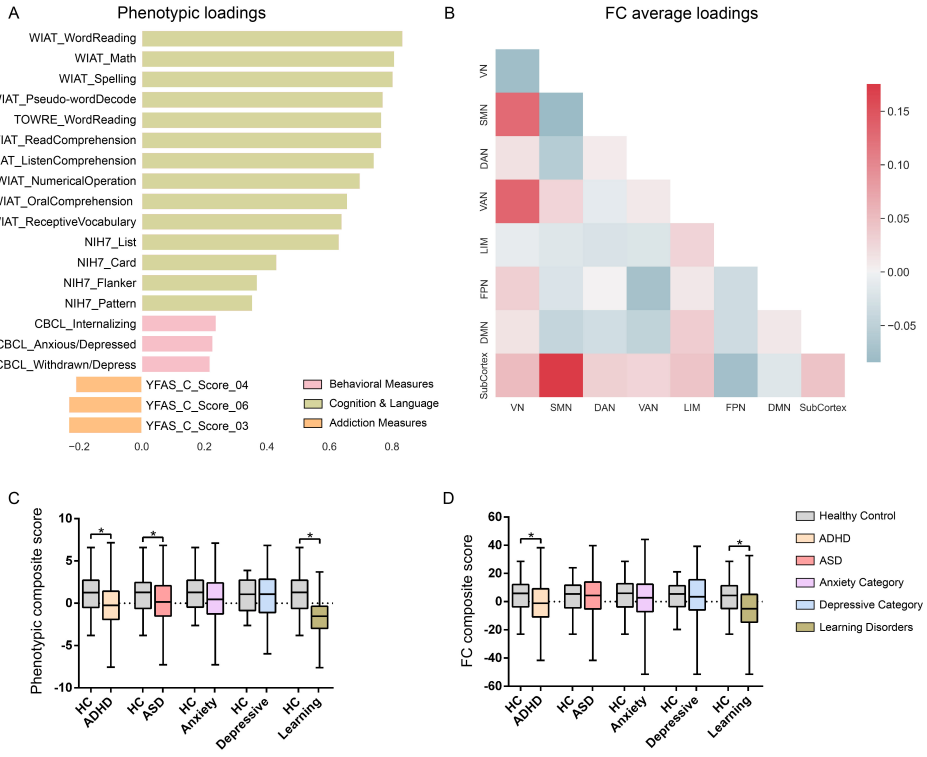

Figure 4: LPP2 - Cognition and Language Skills. **(A)** Phenotypic measures with top 20 absolute values of loadings. Inset shows the color for different type of phenotypic measures. Greater loading in LPP2 was associated with better cognitive and language skills. **(B)** FC loadings averaged within and between 8 networks. The color denotes whether the greater FC is positively (in red) or negatively (in blue) associated with LPP2. **(C)** Group differences in phenotypic composite score between diseases and HC. **(D)** Group differences in FC composite score between diseases and HC. Asterisks indicate significant group difference identified by two-samples t tests or Mann-Whitney U tests ($p < 0.05$). Inset shows the color for diagnostic groups.

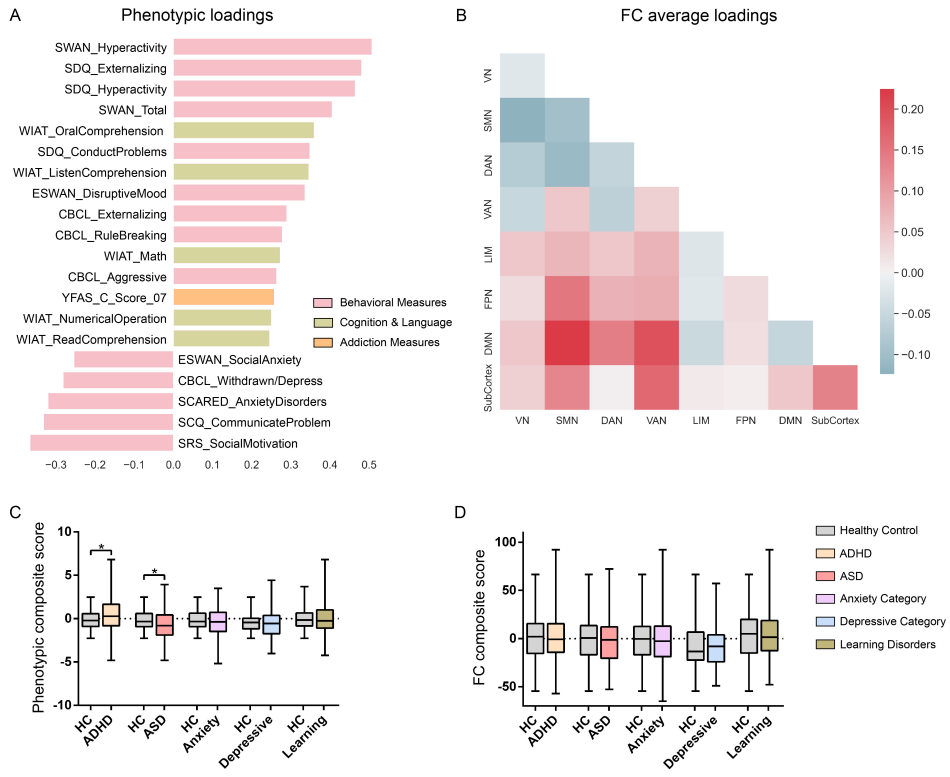

Figure 5: LPP3 - Externalizing Problems. **(A)** Phenotypic measures with top 20 absolute values of loadings. Inset shows the color for different type of phenotypic measures. Greater loading in LPP3 was associated with more externalizing problems. **(B)** FC loadings averaged within and between 8 networks. The color denotes whether the greater FC is positively (in red) or negatively (in blue) associated with LPP3. **(C)** Group differences in phenotypic composite score between diseases and HC. **(D)** Group differences in FC composite score between diseases and HC. Asterisks indicate significant group difference identified by two-samples t tests or Mann-Whitney U tests ($p < 0.05$). Inset shows the color for diagnostic groups.

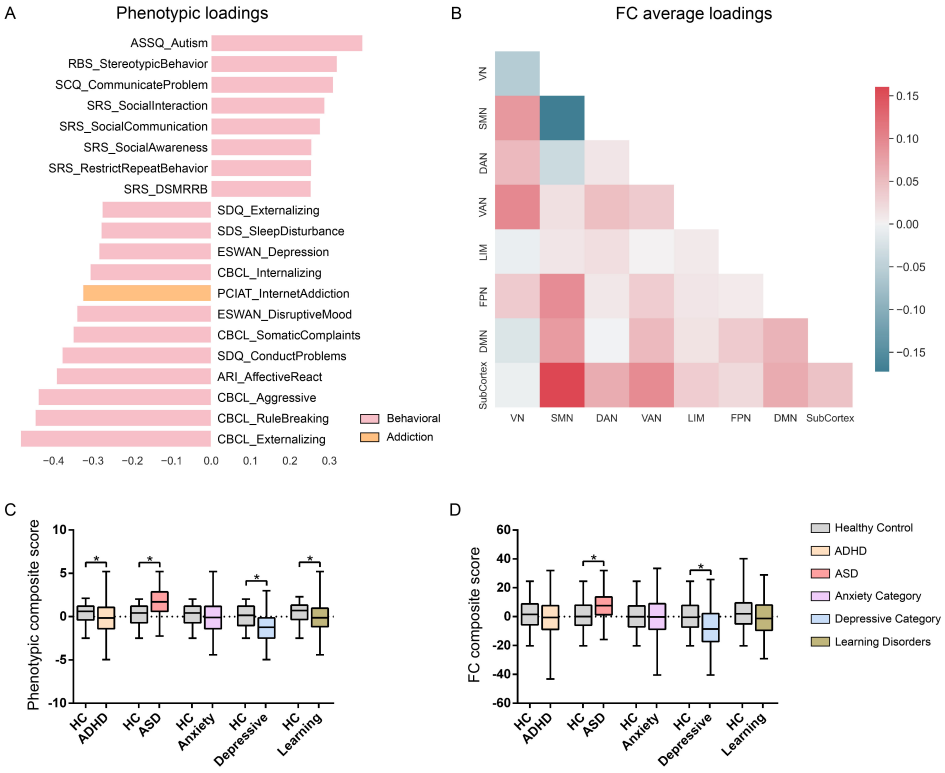

Figure 6: LPP4 - Social Dysfunction. **(A)** Phenotypic measures with top 20 absolute values of loadings. Inset shows the color for different type of phenotypic measures. Greater loading in LPP4 was associated with more social dysfunction and less behavioral problems. **(B)** FC loadings averaged within and between 8 networks. The color denotes whether the greater FC is positively (in red) or negatively (in blue) associated with LPP4. **(C)** Group differences in phenotypic composite score between diseases and HC. **(D)** Group differences in FC composite score between diseases and HC. Asterisks indicate significant group difference identified by two-samples t tests or Mann-Whitney U tests ($p < 0.05$). Inset shows the color for diagnostic groups.

4.1.1 LPP1: General Behavioral Problems

LPP1 ($p = 0.017$, explains 29% of the covariance) reflects general behavioral problems of subjects. Figure 3A shows the 20 most contributory phenotypic measures for this pattern with the highest absolute values of loading, and all these 20 loadings were with significant bootstrapped Z scores. The same phenotypic measure picking strategy was also applied for the other three LPP figures. This phenotypic pattern was composed of many aspects of behavioral problems including social, emotional, and conduct. Higher phenotypic composite score in this pattern is associated with more severe behavioral dysfunction. To clearly depict the correlations of the whole brain FC in 8 networks for each latent FC pattern, loadings of the resting-state FC were averaged across ROI pairs within and between 8 networks (shown in Figure 3B). Higher FC composite score in this pattern is associated with greater FC between the somatomotor network and the ventral attention network, and decreased FC between visual and ventral attention network.

Both phenotypic and FC composite scores of LPP1 were higher in all 5 diagnosed groups compared with an age- and sex-matched HC group, and the difference was significant in all comparisons (Figure 3C, D). This result is consistent with the interpretation that LPP1 is reflecting general behavioral problems.

4.1.2 LPP2: Cognitive and Language Skills

LPP2 ($p < 0.001$, explains 15% of the covariance) dissociated cognitive and language skills. Figure 4A shows the 20 most contributory phenotypic measures for this pattern. All scores of cognition and language assessments involved in the PLS analysis were assigned the top loadings in this phenotypic pattern. Higher phenotypic composite score is associated with better cognitive and language skills. A small number of emotional behavior and addiction measures were also in the top 20 list, but their correlations with the composite score were relatively lower. Figure 4B shows the FC loadings averaged across ROI pairs within and between 8 networks. Higher FC composite score in this pattern is associated with greater FC between somatomotor network and subcortex, as well as greater FC between visual network and somatomotor and ventral attention networks.

Most diagnosed groups had lower phenotypic and FC composite scores compared with their age- and sex-matched HC groups (Figure 4C, D). Both composite scores were significantly lower

in ADHD and learning disorders groups, while ASD group only had significantly lower phenotypic composite scores. In contrast, there was no significant difference on these two composite scores between two emotional disorder groups (anxiety and depressive categories) and HC.

4.1.3 LPP3: Externalizing Problems

LPP3 ($p < 0.001$, explains 10% of the covariance) reflects externalizing problems. The 20 most contributory phenotypic measures for this pattern are shown in Figure 5A. The phenotypic pattern was dominated by externalizing scores (including externalizing, hyperactivity, conduct problem, disruptive mood, rule breaking and aggressive behavior) with positive loadings, while some scores reflecting internalizing problems (anxiety, depressive, and social withdrawal) had the top negative loadings. Besides, 5 scores about cognition and language skills and 1 score about addiction also had relatively high positive loadings. Higher phenotypic composite score is linked with more externalizing problems, and fewer internalizing problems correspondingly. Averaged FC loadings on 8 networks are shown in Figure 5B. Higher FC composite score here is associated with greater connectivity between default mode network and somatomotor network, as well as FC between DMN and ventral attention network.

The phenotypic composite score of ADHD group is significantly higher than its age- and sex-matched HC group, while the score of ASD group is significantly lower than HC group (Figure 5C). In contrast, the FC composite score showed no significant difference between the five diagnosed groups and HC (Figure 5D).

4.1.4 LPP4: Social Dysfunction

LPP4 ($p = 0.015$, explains 4% of the covariance) was driven primarily by social dysfunction, but also involved some emotional and behavioral problems. Figure 6A shows the 20 most contributory phenotypic scores for this latent pattern. All the scores with positive loadings are measuring autism related behaviors, including social responsiveness, restricted interests, and stereotypic behaviors. Phenotypic scores with top negative loadings consisted of both internalizing and externalizing behaviors, along with an internet addiction measure. Higher phenotypic composite score is linked with more severe social dysfunction, and fewer interacting and externalizing behavioral problems. Figure 6B shows averaged FC loadings on networks. Higher FC composite score of this pattern

is linked with increased FC between somatomotor network and subcortex network, as well as decreased within-network connectivity of the somatomotor network.

Figure 6C shows that ASD group had significantly higher phenotypic composite score compared with its age- and sex-matched HC group. On the contrary, the phenotypic composite score is significantly lower in ADHD, depressive and learning disorder groups compared with HC. Besides, Figure 6D shows that ASD group also had significantly higher FC composite score compared with HC, while the group of depressive disorders had significantly lower FC composite score.

4.2 Environmental Moderators for Different Groups

PLS regression analysis identified 4 LPPs that revealed latent relationships between high dimensional phenotypic and functional connectivity data. Next, considering that these relationships may be affected by external factors like parenting style and trauma, moderation analysis was applied to investigate whether some environmental factors are moderating these relationships in some certain groups. To aid presentation of the moderation analysis results, all significant moderators in the 6 groups are summarized by pattern (Figure 7). It is worth noting that in each LPP and in each group of participants, the phenotypic composite score are positively correlated with the FC composite score.

The results of LPP1 (Figure 7A) indicated that corporal punishment and parent distress intolerance (higher tolerance score in Distress Tolerance Scale stands for lower tolerance for distress) promoted the positive impact of this FC pattern on the phenotypic pattern of general behavioral problems in the ASD group, and negative life events promoted the impact in the learning disorder group. On the other hand, poor monitoring had weakened the positive impact of FC on the general behavioral problems of the anxiety group. In the group of depressive disorders, environmental factors including parental inconsistent discipline, father involvement, positive parenting, and negative life events weakened the positive relationship between FC and behavioral problems.

The results of LPP2 (Figure 7B) revealed that parent occupation and involvement are moderating the positive relationship between the second FC pattern and the phenotypic pattern of cognition and language skills in different groups, but their effects vary by group. Parent occupation is weakening the impact of FC on cognition and language skills in ADHD and ASD groups, while it is

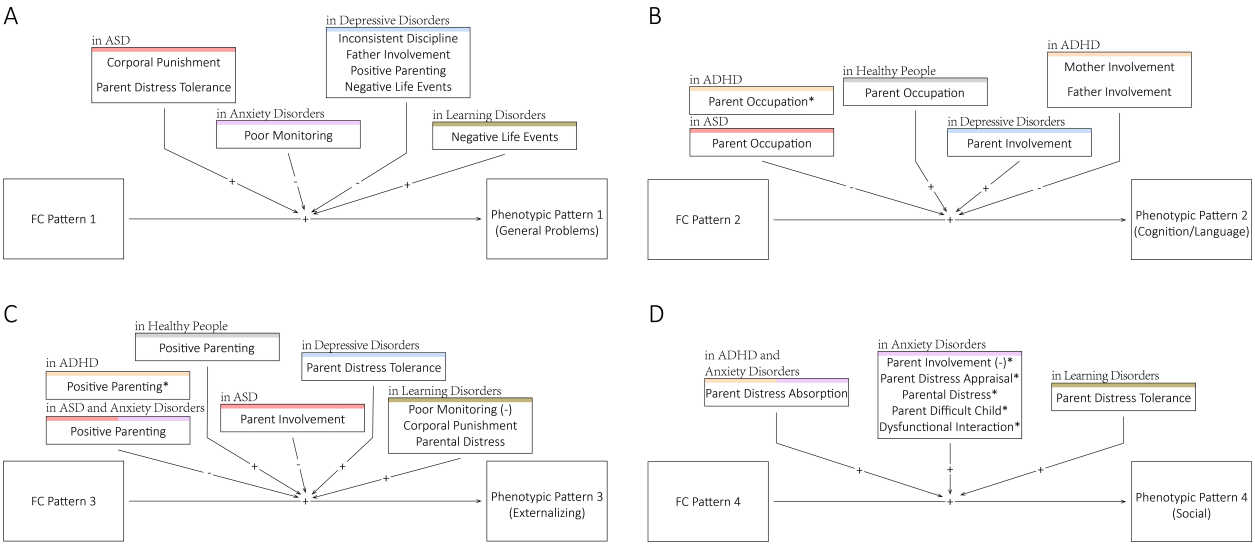

Figure 7: Moderators of different groups in all LPPs. **(A)** The environmental factors moderating the relation between FC and phenotypic pattern of LPP1 in different groups. **(B)** The environmental factors moderating the relation between FC and phenotypic pattern of LPP2 in different groups. **(C)** The environmental factors moderating the relation between FC and phenotypic pattern of LPP3 in different groups. **(D)** The environmental factors moderating the relation between FC and phenotypic pattern of LPP4 in different groups. ”+” between FC and phenotypic patterns denotes the composite scores are positively correlated, ”+” between an environmental factor and the main effect denotes it is strengthening the original correlation, ”-” between an environmental factor and the main effect denotes it is weakening the original correlation. Environmental factors in this figure have significant moderating effect at $p < 0.05$, and ”*” denotes FDR corrected factors.

strengthening the impact in the healthy group. Besides, parent involvement is strengthening the impact in depressive group, while both mother and father involvement scores are showing a weakening effect on it in the ADHD group.

The results of LPP3 (Figure 7C) disclosed the important role of positive parenting for the relationship between this FC pattern and the phenotypic pattern of externalizing problems. Among the three groups of ADHD, ASD, and anxiety disorders, positive parenting had weakened the positive impact of FC on externalizing problems. However, positive parenting strengthened this impact in healthy group. In addiction, parent involvement in the ASD group weakened the impact of FC on externalizing problems, while parent distress intolerance in depressive group strengthening it. In the group of learning disorders, factors including poor monitoring, corporal punishment, and parental distress were also moderators of the relationship.

The results of LPP4 (Figure 7D) indicated that the relationship between its FC pattern and the

phenotypic pattern of social dysfunction in the group of anxiety disorders are moderated by many parental factors. Parent distress appraisal, parent distress indigestion (higher absorption score in Distress Tolerance Scale stands for worse absorption for distress), parental distress, parent difficult child, and Parent-Child dysfunctional interaction are strengthening the positive impact of FC on social dysfunction in the anxiety group, while parent involvement weakened it. Besides, parent distress indigestion in the ADHD group and parent distress intolerance in the learning disorder group also strengthened the impact of FC.

5 Discussion

Utilizing the high dimensional phenotypic and brain functional data from the community-based dataset of HBN, we identified four distinct multivariate latent pattern pairs. The LPPs are respectively representing general behavioral problems, cognitive and language skills, externalizing problems, and social dysfunction across mental illnesses. And the FC latent patterns are distinct brain functional networks associated with the four phenotypic patterns. Each LPP shows disparities between some psychiatric disease groups and healthy control, providing us with a more comprehensive understanding of latent patterns and relationships. Furthermore, in groups with psychiatric disorders, some environmental factors are playing a role of moderator and affecting the correlation between certain brain functional pattern and phenotypic pattern. Combining these findings, the results are indicating that some dimensional transdiagnostic phenotypes are linked with certain patterns of connectivity networks in brain, and they can also be affected by some environmental factors during one's growth, especially for those who have mental illnesses.

5.1 Links From Brain Networks To Phenotypes

The PLS regression have associated general behavioral problems largely with the functional connectivity between somatomotor network and ventral attention network. The SMN is involved in motor control and sensory processing[125, 126], while the VAN is mainly involved in detecting salient stimuli and orienting attention[127, 128, 129]. Interactions between these two brain networks were reported to be abnormal in patients with ADHD[130, 131] and MDD[132]. Since both of these two mental illnesses can lead to serious behavioral or emotional problems[133, 134], this result also supported the

association between the FC latent pattern in LPP1 and general behavioral problems.

In LPP2, the connectivity between SMN and subcortex had the greatest contribution to the FC latent pattern linked to cognitive and language skills. Figure S1B shows that loadings of connections between SMN and the thalamus were carrying the biggest loadings. This result is consistent with previous research demonstrated that the thalamus plays a central role in language and cognition by modulating cortical activity[135], and the functional connectivity between the thalamus and the primary somatosensory cortex is related to cognitive functions[136]. Besides, connections between SMN and VN also played quite important roles in this LPP. Previous studies have consistently demonstrated that the connection in VN-SMN pathway is associated with perception and action[137, 138, 139], and this result shows that it may further affect cognition or language skills.

FC loadings of LPP3 showed that connections between SMN and DMN is very important for one's externalizing behavior. According to previous studies, the functional connectivity between SMN and DMN is decreased in patients with anxiety disorders who have trouble in processing emotional and physical signals[140], but increased in people with functional neurological symptom disorder (FND) who are in a defensive brain-body state that involves prioritizing heightened vigilance and arousal, alterations in pain processing, and increased motor readiness[141]. Another study associated this connection directly with juvenile offenders' impulsive behavior[142]. All these research results are indicating that the connection between SMN and DMN is highly correlated with the regulation ability of the brain in different circumstances. On the other hand, DMN is largely implicated in this LPP, and this is congruent with previous research finding that DMN is crucial for externalizing problems[143].

LPP4 captured both social dysfunction and internalizing and externalizing problems, but in opposite directions. The FC loadings showed that connections within SMN are negatively correlated with the phenotypic latent pattern, which is consistent with a previous finding that functional hypoconnectivity within the SMN is most prevalent in autism[144, 145]. In addition, Figure S1D demonstrated that connections between SMN and thalamus had the biggest positive loadings. It is also in line with a previous study that observed a disconnection between SMN and thalamus in mania and inhibited depression[146].

Furthermore, it is worth noticing that the most important functional connectivities for 4 LPPs all involved the somatomotor network. However, the resting-state functional connectivity about

SMN has been extensively explored in psychiatric research, while the transdiagnostic function of SMN have received relatively little investigation. There have been many case-control studies targeting specific disorder that recorded abnormal resting-state FC involving SMN in patients, including altered connectivities within SMN or between SMN and thalamus in ADHD[147, 148], ASD[147], depression[149], schizophrenia[150, 151, 152, 153, 154, 155], psychosis[156], and bipolar disorder[149, 157, 158, 159]. One recent transdiagnostic study also found that the resting-state FC within SMN is of great importance across multiple phenotypic dimensions[19], and identified SMN as a transdiagnostic hub. The underlying mechanism for such results may be that motor control and sensory processing have potential but more profound impact on phenotypes than we expected. Actually, motor dysfunction was found to be commonly appearing across a number of psychiatric disorders including ADHD, ASD, depression, schizophrenia, bipolar disorder, and Alzheimer's disease[160], and disrupted sensory processing was found in patients with ADHD[161], schizophrenia[162], and bipolar disorders[163, 164]. Some studies have suggested that motor impairments may manifest prior to disease onset and can serve as a prognostic indicator for disease progression[165, 166, 167]. In summary, results of our PLS regression highlight the importance of sensory and motor processes in shaping phenotypes such as cognition, behavior and personality. Uncovering the processing of SMN influencing symptomatology could be of great benefit to future dimensional psychopathology studies.

5.2 Implication of Four Latent Pattern Pairs

LPP1 reflected general behavior problems across several psychiatric diseases. Comparisons between diagnostic groups demonstrated that such general problems are prevalent in mental illnesses, from phenotype to its associated brain networks. Although scores about cognition and language are not involved in LPP1, both phenotypic and FC composite scores are significantly higher in learning disorders. The result may be due to the high proportion of comorbidities in the patient population in this dataset. Indeed, the neural basis for general behavioral problems across categorical diagnoses have long been discussed[10, 13, 14, 15, 168]. The tight link between brain and general behavioral problems may describe the common and intractable behavioral dysfunction caused by brain abnormalities.

Cognitive and language skills of LPP2 and intrinsic neurocognitive network have been investigated from a dimensional perspective[11, 169, 170], and a similar latent pattern was captured in another

data-driven transdiagnostic study[19]. Since that the cognitive impairment and language deficits in neurodevelopmental disorders like ADHD and ASD have long been discussed[171, 172, 173, 174, 175], it is not surprising that composite scores of LPP2 are higher in ADHD and ASD groups. However, the FC composite score difference between ASD and HC is not significant. The reason for such a result may be that the bad performance of ADHD on cognition and language could be caused by their poor attention or weakness in executive functioning[171, 176], while ASD patients are suffering more from communication problems[177, 178], which could have less overlapping on brain activities with LPP2. The relatively small sample size of the ASD group is another possible contributing factor of it.

Externalizing in LPP3, as opposed to internalizing, is a broad classification of childhood behavioral symptoms, describing behaviors such as defiance, impulsivity, disruptiveness, aggression, antisocial features, and overactivity[179, 180]. Similar patterns were also dissociated in other fMRI data-driven transdiagnostic studies[19, 31]. In line with previous research showing a higher incidence of externalizing problems in individuals with ADHD[181, 182, 183] and ASD[184, 185, 186], these two disease groups exhibited higher phenotypic composite scores than HC. However, externalizing behaviors have been extensively documented to be significantly influenced by environmental factors in growth like family[181, 187, 188, 189, 190], leaving FC with relatively weaker association with the behavior outcome. This may explain why FC composite score showed no substantial elevation in ADHD and ASD.

Higher positive scores in LPP4 were indicating greater social dysfunction, leading to increased phenotypic and FC composite score in the ASD group. On the contrast, higher negative score indicated worse behavioral problems, make it more reasonable to see decreased phenotypic composite scores in ADHD, depressive category, and learning groups in this high comorbidity rate community data. There could be multiple factors contributing to the significantly lower FC composite score observed in the depressive group. Firstly, it is widely reported that depressive and internalizing disorders are with a high probability of co-occurrence[191, 192, 193]. On the other hand, thalamus-SMN disconnection found in inhibited depression[146] may also affected the score, but further investigation is needed to understand the neurological origins for behavioral issues in depressive disorders.

5.3 Environmental Moderators for the Brain-Behavior Relations

Moderation analysis have seized multiple environmental moderators of the FC-phenotype relation in LPP1. Considering that LPP1 reflects general behavioral problems including emotional and social issues, this relation can be regarded as the influence of one's brain function to his or her psychiatric disorder outcomes. Parental distress tolerance and corporal punishment in ASD are positively moderating the main effect from FC to phenotypic pattern, indicating that these parental actions may facilitate the expression of behavior problems from the aberrant brain activities in autism. The burden of raising a child with severe and pervasive deficits in ASD placed considerable pressure on the caregiver or parent[194, 195], highlighting the importance of parental capacity to manage distress. Our result is in line with a previous study that suggested a relationship between family adaptability and behavioral problems in children with ASD[196]. Besides, corporal punishment was reported to be related with elevated levels of externalizing behaviors[197], and considered as a strong predictor of behavior problems in children[198, 199]. A harsh parenting style involving the use of corporal punishment in ASD was also found related with more severe externalizing behaviors[200].

It is noteworthy that the brain activity pattern's effect on general behavioral problems in depressive disorders is negatively moderated by four different environmental factors. This result may indicate that positive parenting and the involvement of father can alleviate behavioral problems, primarily internalizing problems, in children with depressive disorders resulting from their abnormal brain functional pattern[192]. On the other hand, both inconsistent discipline of parents[201] and negative life events[202] were reported to be related to externalizing behavior, and they may cause a shift in the behavioral pattern of depressive individuals and drive it away from their brains' destination. Either way, the behavioral problems in depressive disorders are relatively more susceptible to environmental factors in the patient's growth.

In LPP2, only four moderators were found adjusting the relationship between the FC and cognitive and language skills. Parent occupation in individuals with ADHD, ASD, and healthy people, as well as parent involvement in ADHD and depressive disorders, can be considered as conclusive moderators. However, the original FC to phenotype relation were strengthened in healthy and depressive groups, but weakened in patients with neurodevelopmental disorders. Such a difference could be caused by the disrupted neural activities for cognitive control or language compre-

hension in neurodevelopmental psychiatric disorders[203, 204, 205]. In line with our natural thoughts, parent occupation and involvement were both reported to be beneficial for children's cognitive outcome[206, 207, 208, 209]. High family social status and parental involvement may compensate for the lack of cognitive talent in ADHD and ASD patients, which ultimately manifested as a decoupling of brian and phenotypes. In contrast, deficient environmental factors like poverty were associated with bad cognitive attainment[210]. According to our results of group comparisons, patients with depressive disorders have similar cognitive and language abilities to healthy individuals. Good parental occupation and adequate parental involvement for these two groups may prevent them from underdeveloped cognition and language ability, and leading to a performance closer to their natural aptitude.

Positive parenting was long been investigated as one of the most important environmental factor for children's externalizing behavior[211, 212, 213], and showed its moderating effect of brain-externalizing relation among four groups in our results. It may be releasing subjects with ADHD, ASD, or anxiety from their given externalizing tendency[182, 186, 214], as well as eliminating healthy subjects' externalizing behavior induced by undesirable growth environment[187, 215]. Besides, parental distress related factors were also moderating the externalizing behavior of subjects with depressive or learning disorders. Considering that elevated levels of parental stress have been found to be positively associated with increased externalizing behavior problems in children over time[216], this result may suggest that parental distress is increasing the risk of potential externalizing comorbidities in the psychiatric population. Overall, externalizing behaviors is susceptible to environment and can be regulated by parents, even in the ADHD group. This conclusion is also in line with our finding from group comparisons that the brain-behavior association on the dimension of externalizing is relatively weak.

In the group of anxiety disorders, there were as many as 6 parental factors found moderating the relationship between brain functional and phenotypic pattern in LPP4. These moderators are distributed into two aspects, parental distress and parent-child interaction. As the most common anxiety disorder, social anxiety disorder is causing social avoidance in many people[217]. It was reported that parents' response on distress can influence one's social development[218], so does the relationship between parents and children[219]. Factors like parental anxiety and cold parenting are causing the development of social anxiety in their children[220, 221, 222]. In line with these previous

findings, our results indicate that a comfortable family atmosphere and healthy parent-child relationship may prevent anxiety children from developing social anxiety. The relationship between their brain function and social dysfunction situation could than become closer, cause they were facing emotional problems rather social barriers.

In addition to the environmental moderators mentioned above, it is worth noting that some brain-behavior relations are hard to be affected by environment, like cognition and language skills of learning disorders, as well as social problems of ASD. Besides, there are some moderators for some certain groups that have not been mentioned. These environmental factors could affect our brain-behavior relation in similar ways to the discussed factors, or moderating our behavior through an indeterminate path, but a detailed discussion of these specific effects is not the primary objective of us. While the majority of our findings were observed in the vulnerable psychiatric disorder groups, considering that both categorical psychiatric diagnoses and significant moderate effect are determined by some man-made threshold, the moderating effects identified may operate to varying degrees across all populations. Consistent with commonly held beliefs, our results suggest that parents should provide their children with a more stable and harmonious home environment, as well as more positive parent-child interactions.

5.4 Limitations

While this study enjoyed certain advantages such as a substantial sample size and application of advanced multivariate techniques, there are several limitations to be noted. First, the proportion of healthy participants in this dataset is excessively low. The aim of employing PLS analysis on a community-based data was to obtain some brain activity and phenotypic dimensions across diverse populations. Insufficient representation of healthy participants may lead to results that much more generalizable to psychiatric population. Moreover, poor healthy participants also led to small and unbalanced samples in disease and healthy control groups, making the results of group comparisons more deviation sensitive. Future study involving a larger dataset with a more even distribution or a distribution that better reflects the natural morbidity could help correct this bias. Second, effects of age and sex were diluted in our PLS regression. Considering that simple covariate regression cannot thoroughly describe age and sex effects, and the PLS regression is capturing the covarying

patterns, we did not regress age and sex from the data. Fine studies in certain age and sex scopes might help delineate their effects on the brain-behavior relationships. Third, the environmental moderators in different groups and dimensions were not fully explained. Interpretation of the results was hampered by a number of factors, including incomplete perception of the latent patterns, high comorbidities in the dataset, and the mismatch between moderating model and reality. Future studies could incorporate more representative participants and more comprehensive models to improve their guidance for parenting. Besides, most of the environmental moderating effects were not significant after FDR correction. More exhaustive studies of the environmental impact are required to verify the reliability of these results. Finally, only resting-state functional connectivity and limited phenotypic measures were considered in our study. Future research integrating rich multi-modal data is needed for more accurate dissociation of transdiagnostic dimensions.

5.5 Conclusions

To conclude, in this study we identified four associated brain activity and phenotypic pattern pairs from a community-based data. These transdiagnostic pattern pairs showed some overall changes in their related diseases, and the brain-behavior relations between them were found to be moderated by several environmental factors in certain diagnosed groups. Our results suggested that children and teenagers with emotional disorders are relatively vulnerable, the parental factors can change them a lot. Besides, externalizing behavior in mental illnesses can be largely affected by parental factors. A positive parenting style may appease externalizing tendencies in ADHD kids. On the contrary, some intrinsic brain-behavior relationships are much more stubborn, such as inherent cognitive deficits and autistic people's social impairment. Such results and conclusions can help us gain a better understanding of the brain functional basis of psychiatric co-morbidity. More importantly, it is able to provide us with some guidance for the parenting of the children and young adolescent, especially those with psychiatric disorders or some related symptoms.

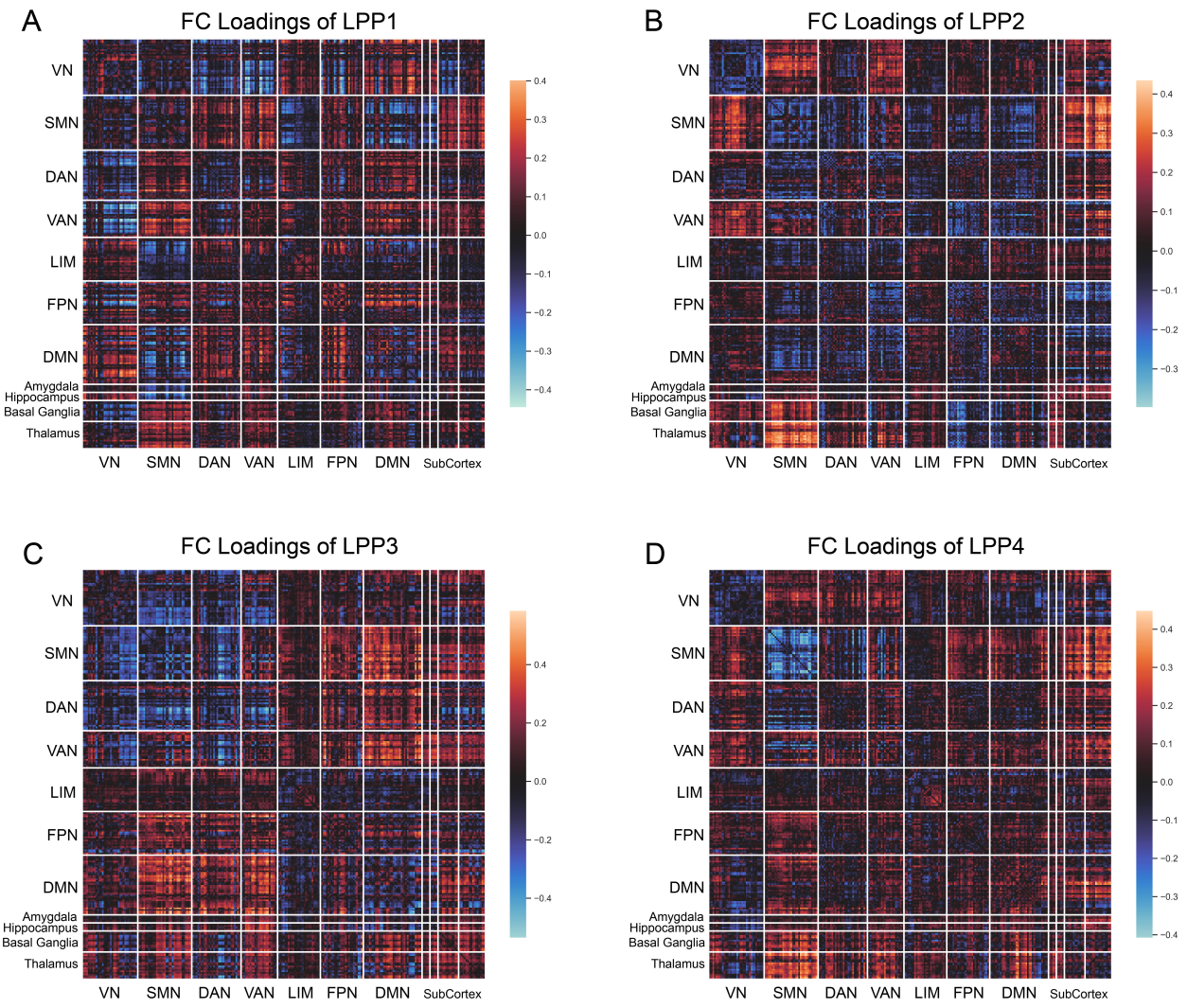

Figure S1: FC loadings of each connection in all LPPs. **(A)** The FC loadings of each connection in LPP1. **(B)** The FC loadings of each connection in LPP2. **(C)** The FC loadings of each connection in LPP3. **(D)** The FC loadings of each connection in LPP4.

6 Supplementary Materials

6.1 Fine Functional Connectivity Loadings of Four LPPs

6.2 Statistical Results of Moderation Analysis

6.2.1 Moderating Effects of Environmental Factors on the Relation of LPP1

Table S1: Moderating Effects of Environmental Factors in LPP1.

p-value* of interaction term significant at 0.05 level.

Group: ADHD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	1.33E-30	0.613
APQ_P_Inconsistent Discipline	0.000	3.07E-32	0.714
APQ_P_Involvement	0.000	3.01E-28	0.613
APQ_P_Poor Monitoring	0.002	6.40E-28	0.332
APQ_P_Positive Parenting	0.000	3.62E-27	0.768
APQ_SR_Corporal Punishment	0.002	1.89E-29	0.331
APQ_SR_Inconsistent Discipline	0.004	4.49E-28	0.150
APQ_SR_Inv_mother	0.001	2.69E-29	0.424
APQ_SR_Inv_father	0.000	8.30E-28	0.702
APQ_SR_Poor Monitoring	0.000	2.72E-27	0.899
APQ_SR_Positive Parenting	0.000	1.71E-28	0.890
Barratt_Total_Edu	0.000	1.00E-28	0.993
Barratt_Total_Occ	0.000	2.04E-28	0.979
DTS_absorption	0.006	7.15E-29	0.079
DTS_appraisal	0.003	4.01E-29	0.173
DTS_regulation	0.003	4.13E-28	0.228
DTS_tolerance	0.003	7.81E-30	0.172
NLES_P_Aware	0.001	2.28E-31	0.487
NLES_P_TotalEvents	0.000	4.64E-31	0.867
NLES_P_Upset_Total	0.001	5.80E-31	0.548
PSI_Difficult Child	0.000	1.37E-63	0.804
PSI_Parent-Child Dysfunctional Interaction	0.000	4.50E-60	0.973
PSI_Parental Distress	0.001	1.00E-40	0.421
Group: ASD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.038	1.33E-05	0.038*
APQ_P_Inconsistent Discipline	0.018	1.86E-07	0.131
APQ_P_Involvement	0.012	6.77E-05	0.253
APQ_P_Poor Monitoring	0.006	1.02E-04	0.428

APQ_P_Positive Parenting	0.000	1.42E-04	0.837
APQ_SR_Corporal Punishment	0.044	2.77E-06	0.022*
APQ_SR_Inconsistent Discipline	0.000	9.91E-05	0.966
APQ_SR_Inv_mother	0.004	1.05E-05	0.468
APQ_SR_Inv_father	0.007	5.27E-05	0.373
APQ_SR_Poor Monitoring	0.003	1.11E-04	0.558
APQ_SR_Positive Parenting	0.006	5.18E-06	0.391
Barratt_Total_Edu	0.000	1.21E-04	0.989
Barratt_Total_Occ	0.001	1.29E-04	0.755
DTS_absorption	0.023	1.23E-05	0.103
DTS_appraisal	0.024	1.80E-05	0.100
DTS_regulation	0.016	4.10E-05	0.177
DTS_tolerance	0.037	1.13E-05	0.039*
NLES_P_Aware	0.010	2.45E-05	0.284
NLES_P_TotalEvents	0.005	4.37E-05	0.460
NLES_P_Upset_Total	0.016	2.76E-05	0.176
PSI_Difficult Child	0.001	1.58E-15	0.687
PSI_Parent-Child Dysfunctional Interaction	0.001	1.93E-12	0.755
PSI_Parental Distress	0.001	2.52E-08	0.777
Group: anxiety category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	1.02E-17	0.733
APQ_P_Inconsistent Discipline	0.006	2.94E-21	0.144
APQ_P_Involvement	0.000	8.34E-17	0.749
APQ_P_Poor Monitoring	0.021	3.75E-17	0.006*
APQ_P_Positive Parenting	0.005	5.59E-16	0.180
APQ_SR_Corporal Punishment	0.003	2.36E-17	0.323
APQ_SR_Inconsistent Discipline	0.010	1.95E-17	0.065
APQ_SR_Inv_mother	0.009	1.26E-16	0.078
APQ_SR_Inv_father	0.000	2.97E-16	0.979
APQ_SR_Poor Monitoring	0.005	1.77E-16	0.175
APQ_SR_Positive Parenting	0.001	1.25E-15	0.580
Barratt_Total_Edu	0.000	9.04E-17	0.912

Barratt_Total_Occ	0.002	1.22E-16	0.437
DTS_absorption	0.001	9.29E-17	0.494
DTS_appraisal	0.000	4.23E-17	0.961
DTS_regulation	0.001	1.49E-15	0.565
DTS_tolerance	0.000	4.32E-17	0.926
NLES_P_Aware	0.001	1.10E-18	0.630
NLES_P_TotalEvents	0.002	6.61E-18	0.399
NLES_P_Upset_Total	0.001	1.33E-18	0.486
PSI_Difficult Child	0.000	3.97E-44	0.912
PSI_Parent-Child Dysfunctional Interaction	0.000	1.33E-44	0.853
PSI_Parental Distress	0.005	5.83E-26	0.171
Group: depressive category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.001	6.81E-07	0.684
APQ_P_Inconsistent Discipline	0.004	1.97E-06	0.477
APQ_P_Involvement	0.003	2.73E-06	0.508
APQ_P_Poor Monitoring	0.027	2.49E-06	0.064
APQ_P_Positive Parenting	0.005	9.69E-06	0.432
APQ_SR_Corporal Punishment	0.003	1.14E-05	0.544
APQ_SR_Inconsistent Discipline	0.032	1.24E-06	0.043*
APQ_SR_Inv_mother	0.027	1.93E-06	0.064
APQ_SR_Inv_father	0.038	6.48E-07	0.026*
APQ_SR_Poor Monitoring	0.030	1.98E-06	0.051
APQ_SR_Positive Parenting	0.040	1.10E-06	0.023*
Barratt_Total_Edu	0.003	8.64E-06	0.565
Barratt_Total_Occ	0.001	6.66E-06	0.708
DTS_absorption	0.000	1.25E-05	0.916
DTS_appraisal	0.001	3.50E-06	0.755
DTS_regulation	0.017	4.81E-06	0.143
DTS_tolerance	0.002	5.46E-06	0.630
NLES_P_Aware	0.037	9.01E-07	0.028*
NLES_P_TotalEvents	0.034	1.30E-06	0.035*
NLES_P_Upset_Total	0.015	5.24E-06	0.164

PSI_Difficult Child	0.006	3.46E-13	0.285
PSI_Parent-Child Dysfunctional Interaction	0.001	4.34E-12	0.717
PSI_Parental Distress	0.007	2.10E-08	0.304
Group: specific learning disorders	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.002	1.24E-18	0.420
APQ_P_Inconsistent Discipline	0.001	7.92E-20	0.542
APQ_P_Involvement	0.008	4.02E-20	0.116
APQ_P_Poor Monitoring	0.001	3.37E-17	0.519
APQ_P_Positive Parenting	0.000	2.61E-18	0.911
APQ_SR_Corporal Punishment	0.001	1.86E-18	0.507
APQ_SR_Inconsistent Discipline	0.001	1.44E-17	0.693
APQ_SR_Inv_mother	0.000	5.45E-18	0.998
APQ_SR_Inv_father	0.000	1.30E-17	0.954
APQ_SR_Poor Monitoring	0.005	9.72E-18	0.214
APQ_SR_Positive Parenting	0.000	1.86E-17	0.925
Barratt_Total_Edu	0.011	1.78E-18	0.071
Barratt_Total_Occ	0.006	3.83E-18	0.178
DTS_absorption	0.000	1.49E-17	0.967
DTS_appraisal	0.000	1.66E-17	0.890
DTS_regulation	0.000	4.04E-17	0.755
DTS_tolerance	0.000	3.18E-18	0.705
NLES_P_Aware	0.014	1.30E-22	0.034*
NLES_P_TotalEvents	0.010	1.25E-21	0.074
NLES_P_Upset_Total	0.010	1.06E-22	0.077
PSI_Difficult Child	0.004	1.86E-41	0.164
PSI_Parent-Child Dysfunctional Interaction	0.000	4.69E-39	0.718
PSI_Parental Distress	0.009	3.60E-26	0.068
Group: healthy	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.035	1.82E-04	0.110
APQ_P_Inconsistent Discipline	0.000	4.19E-08	0.995
APQ_P_Involvement	0.002	2.95E-04	0.692
APQ_P_Poor Monitoring	0.002	9.91E-04	0.710

APQ_P_Positive Parenting	0.001	1.48E-03	0.807
APQ_SR_Corporal Punishment	0.013	2.10E-03	0.356
APQ_SR_Inconsistent Discipline	0.025	1.58E-03	0.196
APQ_SR_Inv_mother	0.008	1.08E-03	0.458
APQ_SR_Inv_father	0.008	2.24E-03	0.453
APQ_SR_Poor Monitoring	0.010	2.26E-03	0.417
APQ_SR_Positive Parenting	0.000	4.91E-03	0.881
Barratt_Total_Edu	0.029	2.58E-04	0.147
Barratt_Total_Occ	0.005	7.03E-05	0.547
DTS_absorption	0.009	2.11E-03	0.448
DTS_appraisal	0.020	3.16E-04	0.228
DTS_regulation	0.003	4.82E-04	0.666
DTS_tolerance	0.002	6.08E-04	0.678
NLES_P_Aware	0.016	7.33E-04	0.295
NLES_P_TotalEvents	0.017	4.17E-04	0.267
NLES_P_Upset_Total	0.004	1.21E-03	0.588
PSI_Difficult Child	0.024	4.73E-08	0.117
PSI_Parent-Child Dysfunctional Interaction	0.010	1.99E-05	0.379
PSI_Parental Distress	0.000	6.11E-05	0.986

6.2.2 Moderating Effects of Environmental Factors on the Relation of LPP2

Table S2: Moderating Effects of Environmental Factors in LPP2.
p-value* of interaction term significant at 0.05 level.

Group: ADHD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.002	2.44E-31	0.320
APQ_P_Inconsistent Discipline	0.000	8.26E-31	0.655
APQ_P_Involvement	0.000	1.74E-30	0.914
APQ_P_Poor Monitoring	0.007	2.56E-31	0.059
APQ_P_Positive Parenting	0.002	4.97E-31	0.359
APQ_SR_Corporal Punishment	0.002	1.06E-31	0.304

APQ_SR_Inconsistent Discipline	0.002	9.57E-31	0.358
APQ_SR_Inv_mother	0.008	2.24E-32	0.040*
APQ_SR_Inv_father	0.012	4.86E-32	0.011*
APQ_SR_Poor Monitoring	0.001	1.34E-30	0.570
APQ_SR_Positive Parenting	0.005	2.01E-32	0.087
Barratt_Total_Edu	0.002	3.10E-34	0.270
Barratt_Total_Occ	0.017	2.68E-33	0.002*
DTS_absorption	0.001	5.05E-31	0.462
DTS_appraisal	0.001	9.92E-31	0.379
DTS_regulation	0.000	1.65E-30	0.735
DTS_tolerance	0.002	4.52E-31	0.325
NLES_P_Aware	0.002	7.61E-31	0.312
NLES_P_TotalEvents	0.001	9.46E-31	0.440
NLES_P_Upset_Total	0.002	8.62E-31	0.338
PSI_Difficult Child	0.000	3.65E-32	0.863
PSI_Parent-Child Dysfunctional Interaction	0.000	1.74E-30	0.861
PSI_Parental Distress	0.001	2.25E-31	0.400
Group: ASD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.001	4.25E-13	0.673
APQ_P_Inconsistent Discipline	0.006	7.15E-12	0.342
APQ_P_Involvement	0.000	4.83E-11	0.868
APQ_P_Poor Monitoring	0.007	3.55E-11	0.312
APQ_P_Positive Parenting	0.000	5.13E-11	0.888
APQ_SR_Corporal Punishment	0.000	1.94E-11	0.900
APQ_SR_Inconsistent Discipline	0.000	6.39E-11	0.790
APQ_SR_Inv_mother	0.004	5.19E-11	0.434
APQ_SR_Inv_father	0.004	4.46E-11	0.410
APQ_SR_Poor Monitoring	0.012	2.53E-11	0.164
APQ_SR_Positive Parenting	0.001	6.33E-11	0.705
Barratt_Total_Edu	0.000	1.37E-11	0.934
Barratt_Total_Occ	0.026	9.07E-12	0.044*
DTS_absorption	0.013	2.56E-11	0.157

DTS_appraisal	0.012	2.71E-11	0.164
DTS_regulation	0.003	5.34E-11	0.504
DTS_tolerance	0.022	1.16E-11	0.064
NLES_P_Aware	0.001	3.49E-11	0.721
NLES_P_TotalEvents	0.010	2.37E-11	0.206
NLES_P_Upset_Total	0.000	5.15E-11	0.986
PSI_Difficult Child	0.001	1.77E-11	0.687
PSI_Parent-Child Dysfunctional Interaction	0.001	6.05E-11	0.700
PSI_Parental Distress	0.000	1.79E-11	0.912
Group: anxiety category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.003	1.81E-24	0.271
APQ_P_Inconsistent Discipline	0.001	3.30E-24	0.578
APQ_P_Involvement	0.000	3.03E-24	0.746
APQ_P_Poor Monitoring	0.001	3.24E-24	0.626
APQ_P_Positive Parenting	0.000	3.01E-24	0.819
APQ_SR_Corporal Punishment	0.002	1.24E-24	0.410
APQ_SR_Inconsistent Discipline	0.000	3.49E-24	0.662
APQ_SR_Inv_mother	0.007	6.71E-25	0.096
APQ_SR_Inv_father	0.001	2.80E-24	0.455
APQ_SR_Poor Monitoring	0.002	2.28E-24	0.320
APQ_SR_Positive Parenting	0.000	1.30E-24	0.670
Barratt_Total_Edu	0.007	7.11E-30	0.071
Barratt_Total_Occ	0.001	9.30E-26	0.612
DTS_absorption	0.002	9.14E-25	0.385
DTS_appraisal	0.001	2.55E-24	0.469
DTS_regulation	0.001	2.99E-24	0.535
DTS_tolerance	0.004	1.33E-24	0.221
NLES_P_Aware	0.001	2.43E-24	0.562
NLES_P_TotalEvents	0.000	3.77E-24	0.870
NLES_P_Upset_Total	0.002	2.49E-24	0.406
PSI_Difficult Child	0.001	4.67E-25	0.508
PSI_Parent-Child Dysfunctional Interaction	0.001	3.06E-24	0.525

PSI_Parental Distress	0.000	1.57E-24	0.666
Group: depressive category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.008	7.45E-11	0.254
APQ_P_Inconsistent Discipline	0.002	1.37E-10	0.578
APQ_P_Involvement	0.040	6.61E-13	0.009*
APQ_P_Poor Monitoring	0.001	1.31E-10	0.745
APQ_P_Positive Parenting	0.004	8.72E-11	0.450
APQ_SR_Corporal Punishment	0.002	1.35E-10	0.556
APQ_SR_Inconsistent Discipline	0.000	3.03E-11	0.828
APQ_SR_Inv_mother	0.000	2.28E-11	0.945
APQ_SR_Inv_father	0.005	1.01E-10	0.351
APQ_SR_Poor Monitoring	0.000	1.65E-10	0.984
APQ_SR_Positive Parenting	0.012	4.96E-11	0.166
Barratt_Total_Edu	0.002	8.09E-12	0.567
Barratt_Total_Occ	0.002	1.07E-10	0.544
DTS_absorption	0.000	1.02E-10	0.924
DTS_appraisal	0.000	2.74E-11	0.828
DTS_regulation	0.001	7.57E-11	0.645
DTS_tolerance	0.001	7.33E-11	0.760
NLES_P_Aware	0.004	7.67E-11	0.407
NLES_P_TotalEvents	0.004	9.82E-11	0.418
NLES_P_Upset_Total	0.001	1.15E-10	0.705
PSI_Difficult Child	0.002	1.29E-10	0.536
PSI_Parent-Child Dysfunctional Interaction	0.001	1.22E-10	0.651
PSI_Parental Distress	0.002	8.70E-11	0.554
Group: specific learning disorders	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.008	9.50E-13	0.150
APQ_P_Inconsistent Discipline	0.003	8.48E-12	0.371
APQ_P_Involvement	0.003	8.82E-12	0.416
APQ_P_Poor Monitoring	0.005	6.48E-12	0.276
APQ_P_Positive Parenting	0.000	1.16E-11	0.983
APQ_SR_Corporal Punishment	0.005	7.53E-13	0.279

APQ_SR_Inconsistent Discipline	0.005	4.70E-12	0.270
APQ_SR_Inv_mother	0.004	6.98E-12	0.295
APQ_SR_Inv_father	0.005	5.07E-12	0.264
APQ_SR_Poor Monitoring	0.000	1.11E-11	0.990
APQ_SR_Positive Parenting	0.002	8.30E-12	0.455
Barratt_Total_Edu	0.001	2.46E-13	0.581
Barratt_Total_Occ	0.000	4.97E-14	0.904
DTS_absorption	0.005	5.70E-12	0.266
DTS_appraisal	0.002	9.33E-12	0.455
DTS_regulation	0.001	1.12E-11	0.594
DTS_tolerance	0.000	1.29E-11	0.979
NLES_P_Aware	0.000	8.09E-12	0.793
NLES_P_TotalEvents	0.001	1.15E-11	0.669
NLES_P_Upset_Total	0.001	1.10E-11	0.578
PSI_Difficult Child	0.000	9.95E-13	0.829
PSI_Parent-Child Dysfunctional Interaction	0.001	1.00E-11	0.647
PSI_Parental Distress	0.000	5.72E-12	0.722
Group: healthy	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	1.29E-03	0.967
APQ_P_Inconsistent Discipline	0.003	1.92E-03	0.660
APQ_P_Involvement	0.000	6.06E-04	0.909
APQ_P_Poor Monitoring	0.004	1.96E-03	0.601
APQ_P_Positive Parenting	0.001	9.06E-04	0.777
APQ_SR_Corporal Punishment	0.024	1.41E-05	0.163
APQ_SR_Inconsistent Discipline	0.011	3.66E-04	0.376
APQ_SR_Inv_mother	0.010	2.48E-04	0.395
APQ_SR_Inv_father	0.023	5.36E-04	0.206
APQ_SR_Poor Monitoring	0.006	3.18E-04	0.500
APQ_SR_Positive Parenting	0.001	6.17E-04	0.816
Barratt_Total_Edu	0.019	2.12E-04	0.243
Barratt_Total_Occ	0.058	1.55E-05	0.033*
DTS_absorption	0.003	2.01E-03	0.653

DTS_appraisal	0.006	1.64E-03	0.515
DTS_regulation	0.010	1.60E-03	0.405
DTS_tolerance	0.001	1.77E-03	0.835
NLES_P_Aware	0.006	1.43E-03	0.525
NLES_P_TotalEvents	0.002	1.57E-03	0.717
NLES_P_Upset_Total	0.010	1.64E-03	0.421
PSI_Difficult Child	0.000	2.14E-03	0.979
PSI_Parent-Child Dysfunctional Interaction	0.001	8.23E-04	0.752
PSI_Parental Distress	0.000	2.01E-03	0.882

6.2.3 Moderating Effects of Environmental Factors on the Relation of LPP3

Table S3: Moderating Effects of Environmental Factors in LPP3.
p-value* of interaction term significant at 0.05 level.

Group: ADHD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	1.88E-21	0.841
APQ_P_Inconsistent Discipline	0.000	3.64E-21	0.719
APQ_P_Involvement	0.007	5.87E-22	0.059
APQ_P_Poor Monitoring	0.003	1.13E-21	0.212
APQ_P_Positive Parenting	0.019	2.97E-23	0.002*
APQ_SR_Corporal Punishment	0.001	2.22E-21	0.589
APQ_SR_Inconsistent Discipline	0.000	1.12E-22	0.914
APQ_SR_Inv_mother	0.001	5.15E-21	0.556
APQ_SR_Inv_father	0.003	2.48E-21	0.241
APQ_SR_Poor Monitoring	0.001	4.99E-21	0.614
APQ_SR_Positive Parenting	0.002	3.61E-21	0.389
Barratt_Total_Edu	0.001	9.49E-24	0.436
Barratt_Total_Occ	0.005	4.42E-24	0.110
DTS_absorption	0.001	4.25E-21	0.566
DTS_appraisal	0.000	1.38E-21	0.943
DTS_regulation	0.001	5.89E-22	0.597

DTS_tolerance	0.006	6.35E-22	0.085
NLES_P_Aware	0.000	5.46E-21	0.664
NLES_P_TotalEvents	0.001	5.25E-21	0.582
NLES_P_Upset_Total	0.000	5.03E-21	0.766
PSI_Difficult Child	0.002	1.55E-21	0.272
PSI_Parent-Child Dysfunctional Interaction	0.005	3.99E-22	0.110
PSI_Parental Distress	0.001	4.31E-21	0.527
Group: ASD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	4.64E-04	0.957
APQ_P_Inconsistent Discipline	0.000	6.45E-04	0.985
APQ_P_Involvement	0.042	1.67E-05	0.029*
APQ_P_Poor Monitoring	0.012	3.32E-04	0.257
APQ_P_Positive Parenting	0.037	6.44E-06	0.039*
APQ_SR_Corporal Punishment	0.001	7.64E-04	0.772
APQ_SR_Inconsistent Discipline	0.007	1.19E-04	0.388
APQ_SR_Inv_mother	0.051	4.15E-05	0.018*
APQ_SR_Inv_father	0.042	3.86E-05	0.030*
APQ_SR_Poor Monitoring	0.016	2.10E-04	0.192
APQ_SR_Positive Parenting	0.014	4.54E-04	0.226
Barratt_Total_Edu	0.015	5.20E-07	0.170
Barratt_Total_Occ	0.020	1.49E-04	0.136
DTS_absorption	0.002	8.39E-04	0.680
DTS_appraisal	0.007	2.40E-04	0.384
DTS_regulation	0.004	2.14E-04	0.521
DTS_tolerance	0.005	5.41E-04	0.461
NLES_P_Aware	0.001	5.45E-04	0.744
NLES_P_TotalEvents	0.004	7.20E-04	0.523
NLES_P_Upset_Total	0.000	9.16E-04	0.947
PSI_Difficult Child	0.009	1.50E-04	0.323
PSI_Parent-Child Dysfunctional Interaction	0.015	4.07E-04	0.199
PSI_Parental Distress	0.001	7.49E-04	0.816
Group: anxiety category	ΔR^2	**F**	**p-value**

APQ_P_Corporal Punishment	0.006	4.19E-16	0.151
APQ_P_Inconsistent Discipline	0.011	1.04E-15	0.055
APQ_P_Involvement	0.001	3.42E-15	0.598
APQ_P_Poor Monitoring	0.002	4.62E-15	0.395
APQ_P_Positive Parenting	0.013	6.33E-16	0.033*
APQ_SR_Corporal Punishment	0.000	3.08E-15	0.967
APQ_SR_Inconsistent Discipline	0.001	1.72E-15	0.582
APQ_SR_Inv_mother	0.003	4.03E-15	0.3200
APQ_SR_Inv_father	0.002	9.69E-17	0.392
APQ_SR_Poor Monitoring	0.000	5.09E-15	0.920
APQ_SR_Positive Parenting	0.002	2.72E-15	0.376
Barratt_Total_Edu	0.001	3.16E-16	0.676
Barratt_Total_Occ	0.001	1.07E-15	0.571
DTS_absorption	0.010	1.40E-15	0.067
DTS_appraisal	0.003	4.76E-15	0.334
DTS_regulation	0.001	4.90E-15	0.507
DTS_tolerance	0.007	1.67E-15	0.129
NLES_P_Aware	0.000	5.15E-15	0.747
NLES_P_TotalEvents	0.001	5.30E-15	0.475
NLES_P_Upset_Total	0.000	7.42E-15	0.903
PSI_Difficult Child	0.009	8.92E-16	0.078
PSI_Parent-Child Dysfunctional Interaction	0.009	1.43E-15	0.075
PSI_Parental Distress	0.006	2.25E-15	0.148
Group: depressive category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.007	7.58E-04	0.379
APQ_P_Inconsistent Discipline	0.002	1.04E-03	0.668
APQ_P_Involvement	0.009	1.09E-03	0.311
APQ_P_Poor Monitoring	0.004	1.29E-04	0.482
APQ_P_Positive Parenting	0.001	9.10E-04	0.808
APQ_SR_Corporal Punishment	0.008	8.53E-04	0.341
APQ_SR_Inconsistent Discipline	0.029	7.78E-05	0.062
APQ_SR_Inv_mother	0.003	1.47E-03	0.567

APQ_SR_Inv_father	0.019	4.75E-04	0.138
APQ_SR_Poor Monitoring	0.008	2.29E-05	0.306
APQ_SR_Positive Parenting	0.000	1.22E-03	0.991
Barratt_Total_Edu	0.004	5.91E-04	0.500
Barratt_Total_Occ	0.001	1.66E-03	0.696
DTS_absorption	0.005	1.04E-03	0.440
DTS_appraisal	0.027	2.94E-04	0.075
DTS_regulation	0.003	1.35E-03	0.555
DTS_tolerance	0.037	1.30E-04	0.037*
NLES_P_Aware	0.004	1.11E-04	0.467
NLES_P_TotalEvents	0.023	2.65E-05	0.096
NLES_P_Upset_Total	0.016	5.85E-04	0.172
PSI_Difficult Child	0.007	1.83E-05	0.346
PSI_Parent-Child Dysfunctional Interaction	0.001	1.30E-03	0.736
PSI_Parental Distress	0.012	3.92E-04	0.235
Group: specific learning disorders	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.006	4.50E-12	0.221
APQ_P_Inconsistent Discipline	0.001	1.13E-12	0.667
APQ_P_Involvement	0.008	1.71E-12	0.155
APQ_P_Poor Monitoring	0.025	6.45E-14	0.011*
APQ_P_Positive Parenting	0.007	3.61E-12	0.179
APQ_SR_Corporal Punishment	0.020	5.40E-13	0.022*
APQ_SR_Inconsistent Discipline	0.001	8.30E-14	0.559
APQ_SR_Inv_mother	0.000	9.28E-12	0.840
APQ_SR_Inv_father	0.003	4.65E-12	0.371
APQ_SR_Poor Monitoring	0.014	4.77E-13	0.057
APQ_SR_Positive Parenting	0.000	7.90E-12	0.945
Barratt_Total_Edu	0.004	1.24E-12	0.334
Barratt_Total_Occ	0.002	1.21E-12	0.474
DTS_absorption	0.000	9.67E-12	0.952
DTS_appraisal	0.001	6.27E-12	0.675
DTS_regulation	0.001	3.24E-12	0.542

DTS_tolerance	0.001	6.61E-12	0.565
NLES_P_Aware	0.001	2.05E-12	0.648
NLES_P_TotalEvents	0.003	3.21E-12	0.367
NLES_P_Upset_Total	0.000	7.81E-12	0.806
PSI_Difficult Child	0.008	6.34E-14	0.134
PSI_Parent-Child Dysfunctional Interaction	0.012	2.17E-13	0.073
PSI_Parental Distress	0.022	1.98E-13	0.017*
Group: healthy	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	6.80E-04	0.967
APQ_P_Inconsistent Discipline	0.007	4.85E-04	0.469
APQ_P_Involvement	0.038	1.91E-04	0.097
APQ_P_Poor Monitoring	0.003	5.69E-04	0.628
APQ_P_Positive Parenting	0.073	2.35E-05	0.018*
APQ_SR_Corporal Punishment	0.001	5.27E-04	0.751
APQ_SR_Inconsistent Discipline	0.004	4.78E-04	0.599
APQ_SR_Inv_mother	0.014	3.20E-04	0.317
APQ_SR_Inv_father	0.006	2.84E-05	0.505
APQ_SR_Poor Monitoring	0.010	4.91E-04	0.397
APQ_SR_Positive Parenting	0.000	7.20E-04	0.967
Barratt_Total_Edu	0.015	3.99E-04	0.310
Barratt_Total_Occ	0.001	6.97E-04	0.813
DTS_absorption	0.000	1.65E-04	0.941
DTS_appraisal	0.050	3.76E-05	0.050
DTS_regulation	0.024	2.97E-04	0.189
DTS_tolerance	0.006	3.90E-04	0.501
NLES_P_Aware	0.003	6.25E-04	0.627
NLES_P_TotalEvents	0.001	5.69E-04	0.803
NLES_P_Upset_Total	0.011	4.64E-04	0.388
PSI_Difficult Child	0.001	3.91E-04	0.766
PSI_Parent-Child Dysfunctional Interaction	0.026	2.60E-04	0.173
PSI_Parental Distress	0.004	6.08E-04	0.578

6.2.4 Moderating Effects of Environmental Factors on the Relation of LPP4

Table S4: Moderating Effects of Environmental Factors in LPP4.
p-value* of interaction term significant at 0.05 level.

Group: ADHD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.004	1.43E-37	0.142
APQ_P_Inconsistent Discipline	0.000	3.69E-40	0.800
APQ_P_Involvement	0.000	1.37E-35	0.927
APQ_P_Poor Monitoring	0.001	8.08E-36	0.465
APQ_P_Positive Parenting	0.000	1.37E-35	0.882
APQ_SR_Corporal Punishment	0.000	9.87E-36	0.937
APQ_SR_Inconsistent Discipline	0.001	4.56E-36	0.494
APQ_SR_Inv_mother	0.001	1.00E-36	0.561
APQ_SR_Inv_father	0.000	6.82E-36	0.805
APQ_SR_Poor Monitoring	0.001	1.70E-37	0.553
APQ_SR_Positive Parenting	0.001	9.87E-36	0.426
Barratt_Total_Edu	0.001	9.27E-36	0.453
Barratt_Total_Occ	0.002	7.27E-36	0.256
DTS_absorption	0.008	5.77E-37	0.033*
DTS_appraisal	0.004	2.05E-36	0.148
DTS_regulation	0.002	8.78E-36	0.338
DTS_tolerance	0.004	1.14E-36	0.139
NLES_P_Aware	0.002	5.10E-36	0.318
NLES_P_TotalEvents	0.003	4.48E-36	0.208
NLES_P_Upset_Total	0.006	1.13E-37	0.070
PSI_Difficult Child	0.004	1.02E-42	0.099
PSI_Parent-Child Dysfunctional Interaction	0.006	2.34E-38	0.055
PSI_Parental Distress	0.004	1.08E-36	0.105
Group: ASD	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.004	9.71E-07	0.488
APQ_P_Inconsistent Discipline	0.002	7.64E-07	0.611

APQ_P_Involvement	0.017	2.13E-06	0.149
APQ_P_Poor Monitoring	0.007	3.56E-06	0.358
APQ_P_Positive Parenting	0.008	5.22E-06	0.330
APQ_SR_Corporal Punishment	0.001	4.35E-06	0.754
APQ_SR_Inconsistent Discipline	0.002	8.24E-06	0.650
APQ_SR_Inv_mother	0.021	1.88E-06	0.113
APQ_SR_Inv_father	0.001	5.09E-06	0.771
APQ_SR_Poor Monitoring	0.004	7.08E-06	0.476
APQ_SR_Positive Parenting	0.000	8.21E-06	0.891
Barratt_Total_Edu	0.005	6.32E-06	0.421
Barratt_Total_Occ	0.027	1.50E-06	0.072
DTS_absorption	0.007	6.68E-07	0.346
DTS_appraisal	0.006	2.84E-06	0.387
DTS_regulation	0.024	1.26E-06	0.087
DTS_tolerance	0.013	1.49E-06	0.205
NLES_P_Aware	0.001	6.08E-06	0.773
NLES_P_TotalEvents	0.001	5.24E-06	0.765
NLES_P_Upset_Total	0.008	2.51E-06	0.330
PSI_Difficult Child	0.000	4.07E-06	0.993
PSI_Parent-Child Dysfunctional Interaction	0.008	5.91E-06	0.339
PSI_Parental Distress	0.014	3.75E-06	0.190
Group: anxiety category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.002	4.21E-22	0.338
APQ_P_Inconsistent Discipline	0.002	2.36E-26	0.355
APQ_P_Involvement	0.019	1.08E-22	0.007*
APQ_P_Poor Monitoring	0.005	2.02E-21	0.185
APQ_P_Positive Parenting	0.000	3.03E-21	0.955
APQ_SR_Corporal Punishment	0.001	4.06E-21	0.480
APQ_SR_Inconsistent Discipline	0.005	6.13E-22	0.150
APQ_SR_Inv_mother	0.001	4.10E-22	0.570
APQ_SR_Inv_father	0.000	2.85E-22	0.780
APQ_SR_Poor Monitoring	0.001	7.54E-22	0.552

APQ_SR_Positive Parenting	0.000	1.34E-21	0.963
Barratt_Total_Edu	0.001	3.61E-21	0.526
Barratt_Total_Occ	0.000	4.72E-21	0.688
DTS_absorption	0.014	2.98E-22	0.019*
DTS_appraisal	0.017	1.71E-22	0.009*
DTS_regulation	0.003	1.57E-21	0.262
DTS_tolerance	0.010	6.49E-22	0.048*
NLES_P_Aware	0.000	6.16E-22	0.903
NLES_P_TotalEvents	0.000	1.78E-21	0.936
NLES_P_Upset_Total	0.002	1.05E-23	0.428
PSI_Difficult Child	0.035	3.31E-29	0.000*
PSI_Parent-Child Dysfunctional Interaction	0.034	2.98E-25	0.000*
PSI_Parental Distress	0.039	9.34E-25	0.000*
Group: depressive category	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.004	2.53E-09	0.465
APQ_P_Inconsistent Discipline	0.001	9.45E-10	0.702
APQ_P_Involvement	0.009	1.90E-09	0.243
APQ_P_Poor Monitoring	0.000	3.34E-09	0.954
APQ_P_Positive Parenting	0.004	3.38E-10	0.456
APQ_SR_Corporal Punishment	0.001	1.42E-09	0.751
APQ_SR_Inconsistent Discipline	0.001	1.25E-09	0.718
APQ_SR_Inv_mother	0.006	1.11E-09	0.358
APQ_SR_Inv_father	0.000	3.10E-09	0.968
APQ_SR_Poor Monitoring	0.007	4.56E-10	0.284
APQ_SR_Positive Parenting	0.001	1.49E-09	0.665
Barratt_Total_Edu	0.002	2.88E-09	0.588
Barratt_Total_Occ	0.002	2.70E-09	0.617
DTS_absorption	0.000	1.50E-10	0.779
DTS_appraisal	0.005	1.65E-10	0.367
DTS_regulation	0.015	4.69E-10	0.126
DTS_tolerance	0.006	4.49E-10	0.333
NLES_P_Aware	0.011	1.34E-09	0.195

NLES_P_TotalEvents	0.008	1.91E-09	0.261
NLES_P_Upset_Total	0.020	7.90E-10	0.079
PSI_Difficult Child	0.000	1.32E-12	0.788
PSI_Parent-Child Dysfunctional Interaction	0.001	1.20E-09	0.655
PSI_Parental Distress	0.009	1.89E-09	0.253
Group: specific learning disorders	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.000	4.39E-15	0.887
APQ_P_Inconsistent Discipline	0.009	3.09E-18	0.103
APQ_P_Involvement	0.005	6.89E-14	0.257
APQ_P_Poor Monitoring	0.004	1.00E-13	0.319
APQ_P_Positive Parenting	0.007	6.73E-14	0.187
APQ_SR_Corporal Punishment	0.001	5.80E-14	0.621
APQ_SR_Inconsistent Discipline	0.004	7.71E-14	0.314
APQ_SR_Inv_mother	0.001	5.32E-14	0.610
APQ_SR_Inv_father	0.001	1.48E-13	0.572
APQ_SR_Poor Monitoring	0.002	7.21E-14	0.498
APQ_SR_Positive Parenting	0.001	1.35E-13	0.558
Barratt_Total_Edu	0.005	9.55E-14	0.249
Barratt_Total_Occ	0.001	1.63E-13	0.607
DTS_absorption	0.005	7.84E-14	0.229
DTS_appraisal	0.009	5.80E-14	0.126
DTS_regulation	0.005	9.38E-14	0.241
DTS_tolerance	0.029	2.74E-15	0.005*
NLES_P_Aware	0.001	1.43E-13	0.658
NLES_P_TotalEvents	0.001	1.24E-13	0.616
NLES_P_Upset_Total	0.003	5.61E-14	0.396
PSI_Difficult Child	0.011	1.63E-16	0.083
PSI_Parent-Child Dysfunctional Interaction	0.009	4.74E-14	0.131
PSI_Parental Distress	0.001	1.48E-13	0.567
Group: healthy	ΔR^2	**F**	**p-value**
APQ_P_Corporal Punishment	0.003	7.54E-04	0.664
APQ_P_Inconsistent Discipline	0.000	5.03E-04	0.854

APQ_P_Involvement	0.019	1.11E-03	0.252
APQ_P_Poor Monitoring	0.004	1.80E-03	0.608
APQ_P_Positive Parenting	0.027	2.69E-05	0.144
APQ_SR_Corporal Punishment	0.015	2.18E-03	0.322
APQ_SR_Inconsistent Discipline	0.025	1.33E-03	0.195
APQ_SR_Inv_mother	0.001	2.87E-03	0.833
APQ_SR_Inv_father	0.001	6.96E-03	0.768
APQ_SR_Poor Monitoring	0.006	8.38E-04	0.508
APQ_SR_Positive Parenting	0.015	4.30E-03	0.317
Barratt_Total_Edu	0.046	4.67E-04	0.073
Barratt_Total_Occ	0.014	1.77E-04	0.309
DTS_absorption	0.001	5.43E-03	0.792
DTS_appraisal	0.022	1.82E-03	0.225
DTS_regulation	0.004	6.09E-03	0.594
DTS_tolerance	0.001	7.03E-03	0.814
NLES_P_Aware	0.007	1.04E-03	0.502
NLES_P_TotalEvents	0.005	2.25E-03	0.558
NLES_P_Upset_Total	0.013	1.43E-03	0.342
PSI_Difficult Child	0.001	5.67E-05	0.739
PSI_Parent-Child Dysfunctional Interaction	0.000	8.83E-06	0.955
PSI_Parental Distress	0.000	6.70E-04	0.998

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