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BSc thesis - Life Science & Technology

Martha Romkes, June 2023

Transdiagnostic Perspectives on ASD and ADHD

Exploring the concept of a phenotypical continuum vs. discrete disorder classifications.

Abstract

This thesis aims to examine the concept of a phenotypic continuum that challenges traditional discrete disorder classifications in neuropsychiatric conditions, particularly autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Comorbidity between ASD and ADHD is frequently observed in clinical practice, and traits associated with these conditions often overlap. The disorders frequently co-occur within families, suggesting similar underlying genetics and biological mechanisms. By analyzing recent genetic research linking gene variants to an increased chance of developing a disorder, this thesis proposes that shared genetic risk factors contribute to a broader phenotypical spectrum encompassing ASD and ADHD and potentially other conditions such as schizophrenia (SCZ) and major depressive disorder (MDD) as well. By understanding the effects and interactions of these genes, genetic analysis has the potential to advance personalized diagnostics and treatment, promoting a shift towards more individualized approaches and a nuanced understanding of neurodevelopmental disorders.

Keywords: autism spectrum disorder, attention-deficit/hyperactivity disorder, comorbidity, genetic risk factors, phenotypic continuum.

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Foreword

In 2013, a significant change was introduced with the release of DSM-5, which merged autistic disorder, Asperger's disorder, and pervasive developmental disorder into a unified diagnosis known as 'autism spectrum disorder' (ASD). This alteration was driven by the recognition that the symptoms of these disorders encompass a continuum of impairments across varying levels of severity, challenging the notion of distinct disorders (American Psychiatric Association, 2013). Before this, it was also not possible to have a dual diagnosis with Aspergers and ADHD, but since the acknowledgement of the disorders' heterogeneity there have been found exceptionally high levels of comorbidity, and overlap in certain traits.

The purpose of the 2013 revision was to enhance the accuracy and precision of ASD diagnosis criteria, facilitating targeted treatments for specific impairments(American Psychiatric Association, 2013). Inspired by this approach, my thesis follows a similar trajectory, guided by recent genetic evidence that suggests the boundaries between different disorders may not be as rigid as initially thought. The overarching research question driving this thesis is as follows: "What are the shared genetic risk factors and underlying biological mechanisms linking ASD and ADHD, and how can this knowledge contribute to the development of personalized diagnostics and more effective treatments?" Central to my hypothesis is the proposition that shared genetic risk factors and underlying biological mechanisms connect ASD and ADHD, positioning ASD as just one dimension within a broader spectrum. The aim of addressing this concept is to shed light on the interconnections between ASD and ADHD, promoting personalized approaches to diagnosis and targeted interventions to improve outcomes and quality of life for individuals affected by these conditions.

Introduction

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are both highly heritable and highly prevalent neurodevelopmental disorders (NDD). ASD is typically characterized by deficits in social communication and interaction, where the presence of restricted, repetitive patterns of behavior, interests, or activities, is also required for diagnosis according to the latest version of the The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association (APA), 2013). ADHD on the other hand is mainly characterized by impaired levels of inattention, disorganization, and/or hyperactivity-impulsivity. The inattention and disorganization that is typical in ADHD involves the inability to stay on task, seeming inattentive, and frequently losing track of belongings. The hyperactivity-impulsivity aspect entails overactivity, and inability to wait. (Tistarelli et al., 2020) Both disorders frequently co-occur and share similarities in certain traits (Rommelse et al., 2010). Investigating the underlying reasons for this co-occurrence and overlap in traits is crucial for a comprehensive understanding of neurodevelopmental disorders.

Trait overlap and heterogeneity

Despite their distinct diagnostic criteria, there is a significant overlap in phenotype between ASD and ADHD. Studies have shown that 20–50% of children with ADHD meet the criteria for ASD, and 30–80% of children with ASD meet the criteria for ADHD (Rommelse et al., 2010). Furthermore, ADHD and ASD appear to often co-occur in families, with one child for instance having ADHD and the other child having ASD or a combination of both disorders. Besides their high comorbidity, there are notable similarities in their core symptoms. The symptoms of ADHD, such as attention deficit and impulsivity can also be observed in individuals with ASD (Hours et al., 2022). In turn, the communication deficits that are commonly associated with ASD can also be present in individuals with ADHD (Leitner et al., 2014). Another direct association between ASD and ADHD traits can be found between hyperactivity and stereotyped, repetitive behaviors (Sokolova et al., 2017). These shared traits suggest the involvement of common neurobiological mechanisms related to executive functioning, attention, and reward systems (Christakou et al., 2013). The relationship between ASD and ADHD traits has been proposed to be primarily influenced by shared attention-related problems, like inattention and attentional switching capacity, which would suggest that the genetic causes of these disorders may involve biological pathways related to attentional control (Polderman et al., 2013). A study conducted by Taylor et al. (2015) instead indicated that the genetic overlap between ASD and ADHD is strongest in relation to communication difficulties, while repetitive behavior and social difficulties exhibit only moderate genetic overlap (Taylor et al., 2015). These diverse findings highlight the complex nature of the comorbidity between ASD and ADHD, suggesting the involvement of multiple factors in their co-occurrence. Given the high heterogeneity observed in both disorders, it is plausible that individuals may present with unique combinations and varying degrees of symptom severity. Consequently, studies investigating risk genes associated with ASD and ADHD could benefit from adopting a symptom-specific approach (Taylor et al., 2015), recognizing the importance of tailoring research to account for the individuality of symptom presentations rather than grouping all individuals with the same diagnostic label into a single category.

From childhood schizophrenia to a continuous spectrum.

The perception of autism has evolved significantly over time, from its early association with childhood schizophrenia to the recognition of a continuous spectrum. In the second edition of the DSM published in 1968, autism was initially described as a form of childhood schizophrenia caused by cold parenting (APA, 1994). However, this notion was later disproven in the 1960s and 1970s (Zeldovich, 2018). The concept of autism expanded further in the 1990s with the inclusion of pervasive developmental disorder-not otherwise specified (PDD-NOS) as a milder version of autism, indicating the existence of a spectrum. It wasn't until the fourth edition of the DSM in 1994 that autism was officially categorized as a spectrum. This edition listed five conditions, including autism, PDD-NOS, Asperger's disorder, childhood disintegrative disorder (CDD), and Rett syndrome (APA, 1994). The spectrum encompassed a range of features and

severity levels, with the milder end involving cases without intellectual disability or severe impairments.

The transition to the current understanding of autism as a spectrum occurred for two primary reasons. First, there was a concern about the lack of consistency in diagnosing autism, with variations among clinicians leading to different labels such as Asperger's or PDD-NOS for the same individual (Zeldovich, 2018). Second, after the completion of the Human Genome Project in 2003, numerous studies aimed to identify specific genes linked to autism. Although hundreds of risk genes have been discovered, none of them could be exclusively linked to a particular classification within the spectrum (Rylaarsdam et al, 2019). This realization highlighted the broader and more heterogeneous nature of the disorder. Because of this, it was decided that characterizing autism as an all-inclusive diagnosis, spanning from mild to severe, would be more accurate and reflective of the complex nature of the condition.

SFARI gene database and EAGLE

Since the human genome project, many more studies have been conducted in attempts to identify risk genes associated with autism and other neuropsychiatric conditions. Especially for autism, there is a large body of data on associated gene variants available. The data used in this thesis was extracted from SFARI gene, a comprehensive database which is maintained by the organization SFARI (Simons Foundation Autism Research Initiative), which is a nonprofit organization dedicated to advancing scientific research on ASD. The online database provides information on genes implicated in ASD and related neurodevelopmental conditions, and was designed to help researchers track the ever-expanding genetic risk factors that emerge in the literature. Their human gene module currently lists 1, 231 genes implicated in autism, each of which have dedicated entry pages with information regarding the amount of reports, rarity, associated syndromes and disorders, and a gene score that assesses the strength of the evidence for each gene’s association with ASD.

For the analysis of overlapping genetic risk factors, the human gene model is used, focusing specifically on gene variants with a high EAGLE score. The EAGLE (Evaluating Annotations of Genes for Links to phenotypes using GWAS and eQTLs) scoring system was developed as multi-disciplinary consensus-based method for the curation of genes associated with likelihood to develop ASD. A high EAGLE score confirms a gene’s relationship with ASD, but does not rule out a relationship with any other neurodevelopmental phenotypes, making genes with a high evidence score that was curated with the EAGLE scoring framework a useful source for researching genetic overlaps between neurodevelopmental disorders. Genes with an EAGLE score >12 have been repeatedly implicated in ASD across independent publications, providing robust and consistent support for their involvement, and no substantial evidence has emerged that contradicts the established role of these genes in ASD. (EAGLE Score - SFARI Gene, n.d.)

Overlapping risk genes

The SFARI gene database not only curates and ranks evidence, but also tracks studies on these genes and their associations with various disorders. Among the top-ranking risk genes in terms of their EAGLE score, all falling within the high confidence category, clear implications in ASD have been established based on the presence of multiple de novo likely-gene-disrupting mutations reported in the literature. Notably, many of these genes demonstrate associations not only with ASD but also with several other neurodevelopmental disorders (NDDs), with the top four genes also having and established association with ADHD (see Table 1). The shared heritability between both disorders strongly indicates the existence of pleiotropic genes involved in ASD, ADHD, or the combination of both (Rommelse, 2011).

Gene-symbol	Eagle score	Associated disorders
NRXN1	143,75	SCZ, DD/NDD, ADHD, ID, EP, BPD, EPS, ASD
SCN2A	109,3	DD/NDD, ADHD, ID, EP, EPS, ASD
MECP2	106,65	SCZ, DD/NDD, ADHD, ID, EP, EPS, ASD
CHD8	97,65	SCZ, DD/NDD, ADHD, ID, EPS, ASD
SHANK3	74,85	DD/NDD, BPD, ID, EPS, ASD

Table 1. Top 5 genes (based on the EAGLE scoring system) associated with ASD. Source: SFARI gene, 2023)

While the current number of genes with established associations between ASD and ADHD is already substantial, recent genetic studies across different disorders suggests that this number may increase significantly in the future. For instance, genes such as SHANK2 (related to, but different from SHANK3), KDM6B, and FOXP1, all have an assigned EAGLE score over 12 () and are thus already strongly linked to ASD. To this date, these three genes are not established to have an association with ADHD according to the SFARI database, but recent studies indicate otherwise.

In the case of SHANK2, Ma et al. found no significant differences in allele frequency of specific single nucleotide polymorphisms in SHANK2/SHANK3 among clinical groups of children with ADHD, ASD, or both (Ma et al., 2021). Additionally, a study from 2017 even revealed a link between SHANK2 and not only ASD and ADHD, but schizophrenia as well (Pappas et al., 2017). This observed overlap in occurrence among seemingly distinct disorders suggests a biological interconnectedness and the potential of SHANK2 to is considered to be a possible candidate (Ma et al., 2021). Pleiotropy refers to the phenomenon where a single gene can influence multiple traits or have effects on multiple organ systems. In the context of neurodevelopmental disorders, pleiotropic shared genes may contribute to the manifestation of diverse phenotypes across different conditions. The presence of such shared genes implies common underlying molecular pathways and mechanisms that transcend diagnostic boundaries.

Understanding these pleiotropic genes and their impact on multiple traits can provide valuable insights into the complex nature of neurodevelopmental disorders and facilitate the development of targeted interventions that address shared biological pathways.

KDM6B (Lysine Demethylase 6B) is another gene which was already known for its association with neurodevelopmental disorders, but has recently emerged as the highest-ranking known risk gene for the comorbidity between ASD and ADHD. (Zhou et al., 2023). Deletion of a KDM6B allele in mice has led the mice to present with ASD/ADHD-like behavioral deficits, like impaired sociability and object recognition memory which is characteristic for ASD, but also increased locomotor activity and impulsivity, two ADHD-like behavioral traits (Gao et al., 2022).

Lastly, FOXP1 (forkhead box P1), is a gene belonging to a family of transcription factors that are involved in the regulation of tissue- and cell type-specific gene transcription (NCBI, 2023). Investigations into phenotypical variants resulting from FOXP1 mutations found that these mutations were characterized by a range of behavioral features that are characteristic of ASD, ADHD, and anxiety disorders (Trelles et al., 2021). Amongst the participants in this study, 71 % received a consensus diagnosis with ADHD, while only 24% of participants met criteria for a consensus diagnosis of ASD. Considering that these 3 genes were originally implicated with just ASD (and currently still lack an established association with ADHD in SFARI gene), this suggests that the number of overlapping or pleiotropic genes is likely to increase in the future.

The genetic overlap among various disorders and psychiatric conditions is further supported by studies that have conducted genetic correlations comparing the genomic profiles of different conditions. Figure 1 provides a visual representation of these genetic correlations, demonstrating that ASD shows the highest genetic correlation with ADHD. Notably, at a broader level, disorders such as major depressive disorder (MDD), anxiety disorders (ANX), ADHD, ASD, and post-traumatic stress disorder (PTSD) cluster together, highlighting their genetic inter-correlation (Cao et al., 2022). These results shed light on the high comorbidity observed

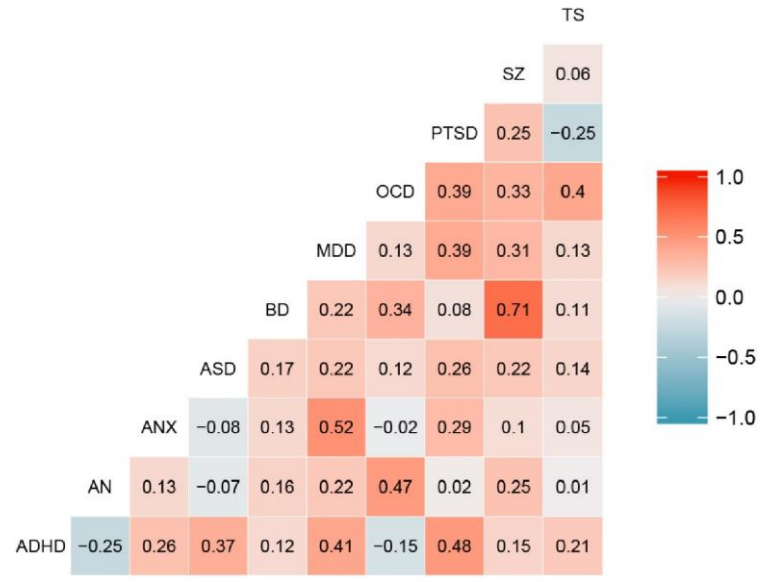


Figure 1. Genetic correlation between mental disorders. Source: Cao et al.,2022

Abbreviations: Attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), anxiety disorder (ANX), autism spectrum disorder (ASD), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), schizophrenia (SZ), and Tourette syndrome (TS)

among these conditions, suggesting that while these disorders can be distinguished based on their specific psychopathology, they also share underlying genetic factors contributing to their co-occurrence.

The discovery of shared genes across different neurodevelopmental disorders implies an inherent overlap and genetic intercorrelation of psychiatric traits. As additional genetic sequencing studies continue to unfold, the number of genes implicated across multiple disorders is likely to expand, deepening our understanding of their underlying genetic architecture and biological mechanisms. This idea is supported by Ghirardi et al, who demonstrated the existence of a genetic overlap between clinical ASD and ADHD through twin studies, and suggests that previous genomic studies may have underestimated the genetic overlap between the two disorders (Ghirardi et al., 2017). Continued research in this area will enhance our understanding of the complex genetic landscape and potentially reveal new therapeutic targets for these challenging conditions..

Neurobiological functioning of top genes

Identifying top genes is crucial, but understanding their molecular functioning and corresponding biological mechanisms may be even more important in order to gain insight into how these genes may influence the traits and characteristics associated with neurodevelopmental disorders. For this reason the top 5 associated ASD risk genes are analyzed in terms of their molecular functioning.

NRXN1 (neurexin 1), which is known for recurrent mutations in individuals with ASD, encodes neurexins, a family of cell adhesion molecules and receptors that play a crucial role in synaptic function in the vertebrate nervous system (NCBI, 2023). Dysregulation of this gene can disrupt synaptic connectivity and neuronal signaling, and several mouse models have shown that deletion of neurexin genes induced behaviors reminiscent of ASD phenotypes (Khoja et al., 2023).

The SCN2A (sodium voltage-gated channel alpha subunit 2) gene codes for the voltage-gated sodium channel, that is essential for generating and propagating action potentials, particularly in nerve and muscle cells (NCBI, 2023 ; Kruth et al., 2020). It is one of the most common genes associated with autism-causing mutations, has been identified to have both gain-of-function and loss-of-function mutations in humans, leading to distinct phenotypes such as epilepsy and autism/intellectual disability. This makes this gene useful in studies comparing the effects of different variants. Understanding the role of SCN2A in neural development and function may contribute to the development of therapies for SCN2A-related diseases like epilepsy, which can be challenging to treat effectively (Kruth et al., 2020).

The MECP2 (methyl-CpG binding protein 2) gene encodes the MeCP2 protein which is involved in transcriptional regulation (NCBI, 2023). A mutation in this gene is the cause for most cases of Rett syndrome, a neurodevelopmental disorder classified as an autism spectrum disorder characterized by psychomotor regression, loss of hand use and spoken language, repetitive hand stereotypies, and gait impairment. An interesting aspect of this syndrome, is that

is has been proven to be reversible in mouse models, providing inspiration and hope that such a goal may be achieved for RTT in humans and potentially for many other neurodevelopmental disorders (Neul, 2012).

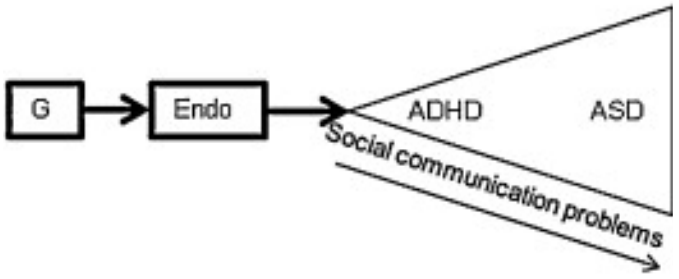
CHD8 (chromodomain helicase DNA-binding protein 8) is a chromatin remodeler (NCBI, 2023) associated with autism spectrum disorders. Studies using Chd8 knockout mice showed that deletion of CHD8 in neocortical glutamatergic neurons leads to apoptosis-dependent near-complete elimination of neocortical structures, and distinctly alters cognitive behaviors and sensory-motor functions in these mice (Kweon et al., 2021). The elimination of neocortical structures distinctly affects cognitive behaviors and sensory-motor functions in mice, while macrocephaly associated with Chd8 haploinsufficiency may represent compensatory responses. These findings suggest that CHD8 plays a critical role in neocortical development through anti-apoptotic mechanisms (Kweon et al., 2021).

Lastly, the SHANK3 (SH3 and multiple ankyrin repeat domains 3) gene, a member of the Shank family of synaptic proteins, encodes a protein that functions as a molecular scaffold in the postsynaptic density of excitatory synapses. It plays a crucial role in synaptic structure formation and function, facilitating protein-protein interactions and modulating the molecular organization of the postsynaptic densities in the brain (NCBI, 2023). Shank3 knock-out mice showed dysfunction in synaptic transmission, behavior, and development (Amal et al., 2020), again underscoring this gene's involvement neurodevelopmental disorders.

The biological mechanisms associated with these genes provide insights into how they may contribute to the traits associated with ASD, ADHD, or both. The aforementioned genes play crucial roles in synaptic function, neuronal signaling, chromatin remodeling, transcriptional regulation, and synaptic structure. Dysregulation or alterations in these genes can disrupt synaptic connectivity, impair neural activity, influence gene expression patterns, and disrupt synaptic organization, all of which may contribute to the characteristic traits observed in individuals with ASD and ADHD. Understanding these biological mechanisms helps us gain a deeper understanding of the complex interplay between genetic factors and the manifestation of clinical symptoms in neurodevelopmental disorders. It also provides potential targets for therapeutic interventions aimed at improving the outcomes and quality of life for individuals affected by these conditions. However, due to the remarkable heterogeneity of ASD and ADHD, a deeper phenotypic characterization is imperative to ascertain how the complex underlying genetics influence cognition, behavior, and the presence of co-occurring conditions within the autism spectrum (Warrier et al., 2022). Further research is needed to unravel the specific genetic mechanisms and interactions that contribute to the observed genetic overlap and to explore how they influence the clinical presentation and course of these disorders.

Distinct disorders vs. continuous spectrum

Several studies have proposed that instead of distinct disorders, ASD and ADHD are different manifestations of a broader, overarching disorder (van der Meer et al., 2012 ; De Groot et al., 2017). These researchers hypothesized the existence of a single continuum, exploring the idea of a broader framework that encompasses the heterogeneity observed in these conditions (van der Meer et al., 2012). Rommelse discussed a hypothetical model where individuals with ADHD exhibit a range of social and communicative impairments, progressing towards the more severe end of the spectrum characterized by ASD, which manifests as the most severe subtype with additional pronounced social difficulties (See Figure 2) (Rommelse et al., 2011). This perspective suggests that the genetic basis underlying both ADHD, ASD, and a comorbid version of both disorders, may be largely overlapping, with variations in severity attributed to environmental factors or additional risk alleles specific to ASD and their interactions with environmental factors. This model challenges the notion of distinct disorders and supports the concept of a phenotypic continuum, with varying degrees of manifestation and impairment, emphasizing the need for a comprehensive understanding of the underlying genetic and environmental factors influencing this continuum.



Model 2. ASD and ADHD are different manifestations of the same overarching disorder. The manifestations range from ADHD with few if any social handicaps and problems through ADHD with greater levels of social and communicative problems, to ASD as the most severe subtype characterized by additional more severe social problems.

Figure 2. Overarching disorder model where the severity of social communication problems forms the main distinguishing factor. Source: Rommelse et al., 2011

Perception of disability

The understanding of autism spectrum disorder (ASD) is evolving, prompting a reassessment of the traditional concept of disorder and its application to individuals with certain traits or gene variants. Studies have shown that a significant number of individuals who are not diagnosed with ASD still exhibit autistic traits (De Groot et al., 2017). This indicates that the spectrum of autism includes individuals from the general population, highlighting the presence of autism-related traits across a wide range of individuals. A study conducted by Kushki et al. further supported this idea by clustering individuals with ASD, ADHD, obsessive-compulsive disorder (OCD), and typical development (TD) based on neuroanatomical similarities and genomic profiles (Kushki et al., 2019). The results (See Figure 3) showed overlaps in neuroanatomy and genomic profiles not only among different neurodevelopmental disorders but also among typically developing individuals, suggesting the existence of a phenotypic continuum where

traits and gene variants associated with these disorders can be present without a formal diagnosis.

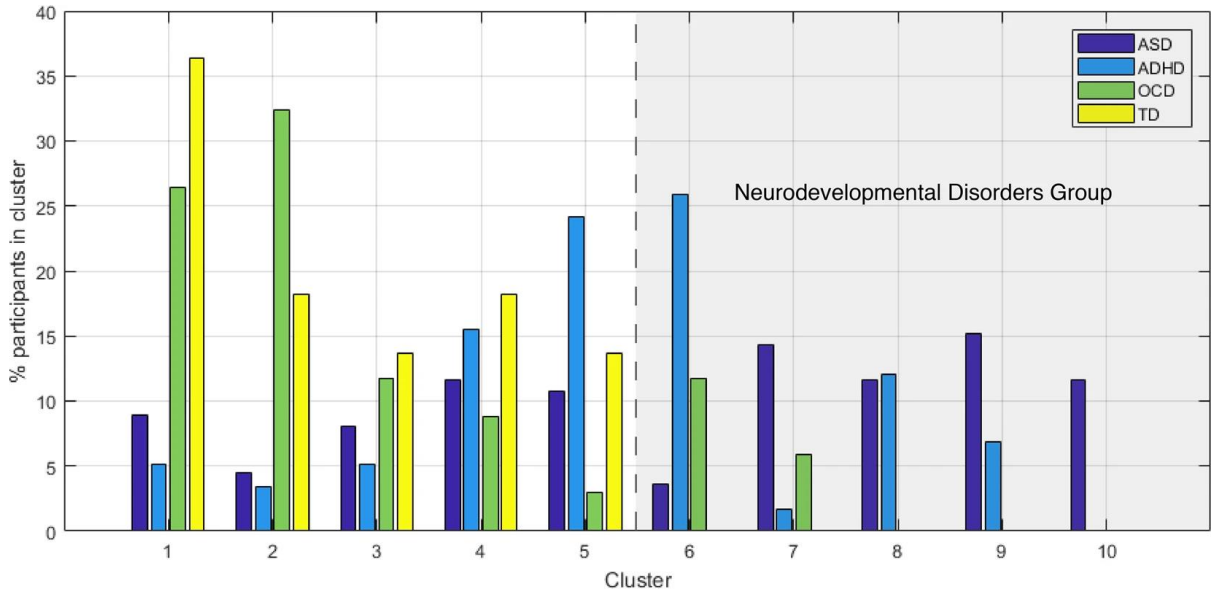


Figure 3. Percentage of participants from four diagnostic categories (ASD, ADHD, and TD) in each cluster. Source: Kushki et al., 2019

Traditionally, ASD has been associated with intellectual disability, yet it represents only a subset of cases, accounting for approximately 30% of ASD diagnoses (Iossifov et al., 2014), and this form of ASD appears to be linked to de novo mutations rather than inheritable variants. In contrast, the more prevalent form, often referred to as "high-functioning autism," is not associated with intellectual disability. It is highly heritable and has been observed to occur more frequently among individuals in certain scientific professions, such as physicists, engineers, and mathematicians (Baron-Cohen, 1998). The association between autism traits and scientific skills has been further supported by studies utilizing the "Autism quotient" to measure the severity of ASD symptoms. Researchers found that scientists, particularly mathematicians and physicists, scored significantly higher on this scale compared to students in the humanities and social sciences, indicating a correlation between autistic traits and scientific abilities (Baron-Cohen et al., 2001). Additionally, investigations into the genetic basis of ASD have revealed that common alleles associated with an increased risk of ASD demonstrate a signature of positive selection in European populations (Polimanti et al., 2017). These findings suggest that at least some of the genes implicated in ASD may confer an evolutionary advantage. These insights into the heterogeneity of ASD and its association with specific skills and genetic factors raise important questions about the suitability of the term "disorder". Not every individual with ASD will perceive their condition as disabling, and it might be more appropriate to opt for a more nuanced perspective that recognizes the continuum of autism and the unique experiences and strengths of individuals along this spectrum.

Future applications

The identification of shared genes across different disorder and conditions emphasizes the importance of adopting a dimensional approach to psychopathology, and challenges the traditional notion of strict diagnostic boundaries. By harnessing the expanding data on risk genes and genetic intercorrelation, researchers can uncover the pleiotropic effects of genes, where a single gene influences multiple traits simultaneously. This multidimensional, transdiagnostic perspective provides a more nuanced understanding of the complex nature of psychiatric disorders. Moving away from reliance solely on diagnostic labels, researchers can gain a more comprehensive understanding of the underlying mechanisms contributing to psychiatric disorders by shifting the focus towards phenotypic data and gene variants. This paradigm shift enables more accurate and personalized assessments, facilitating targeted interventions tailored to individuals' specific traits and needs. the current advances in genetic and molecular research already hold great potential for future diagnostics and treatment. Genetic screening for example could revolutionize detection and diagnosis by identifying harmful gene variants associated with these disorders. This genetic screening would also enable the development of treatment or therapy optimized for specific genetic profiles. Ideally, genetic screening should be complemented with comprehensive psychological questionnaires to capture corresponding phenotypic information. This in turn would add to the existing body of research aiming to identify the specific biological pathways through which certain traits arise. Achieving these goals necessitates multi-disciplinary collaborations across genetics, neuroscience, psychology, psychiatry, and related fields to develop holistic treatment approaches. However, further research, validation, and ethical considerations are imperative to fully unlock the potential of these future applications and ensure their positive impact on individuals affected by neurodevelopmental disorders.

Discussion

While the shift from 'subtypes' to the 'autism spectrum' acknowledged the heterogeneity of ASD, the multitude of different risk genes suggests that the isolated approach to this disorder may limit individualized treatment approaches. The presence of shared gene variants across disorders, suggests that these conditions may represent different expressions or combinations of underlying genetic abnormalities, where the observed behavioral phenotypes serve as observable markers of the underlying biological mechanisms at play. Different individuals may exhibit varying degrees and combinations of symptoms due to their unique genetic profiles.

From a genetic standpoint, these findings depict these seemingly separate disorders as interconnected, where only the resulting behavioral phenotypes and observable traits can be distinguished from another. The shared underlying biological mechanisms may mean that the boundaries between different disorders are not as rigid as initially thought. Instead, it is more likely there exists a complex interplay of genetic factors that can contribute to the manifestation of various neuropsychiatric conditions. A specific manifestation of a ‘disorder’ may arise due to either a combination, accumulation, or interaction of specific gene variants, and patients with

similar pathogenic variants may be diagnosed on very different levels of the spectrum (Rylaarsdam et al., 2019).

An important limitation to consider is the potential bias or limited coverage inherent in the gene database utilized in this study. Specifically, certain genes were reported to be associated with ADHD in the literature, but this association was not acknowledged by the SFARI gene database at the time of analysis. This discrepancy has the potential to introduce limitations to the conclusions drawn from the data, as the database's content and categorization may not fully capture the entire spectrum of genetic overlap. Additionally, it is worth noting that the focus of this study was primarily on ASD and ADHD, and the analysis did not encompass the full breadth of neurodevelopmental disorders. While there is a significant body of literature addressing genetic overlaps and comorbidity among various neurodevelopmental disorders, the constraints of time and resources prevented an extensive analysis beyond the scope of ASD and ADHD. However, it is important to acknowledge the possibility of genetic overlap and comorbidity with other neurodevelopmental disorders, and further research is warranted to explore these associations in depth.

Conclusion

Considering the substantial heterogeneity observed within ASD and ADHD, along with their high comorbidity rates and shared genetic risk factors, it is increasingly evident that these conditions, and potentially other neurodevelopmental or neuropsychiatric disorders, may extend beyond their currently defined boundaries. Rather than viewing ASD as a discrete spectrum, it is more accurate to conceptualize these disorders as existing on a larger, multidimensional spectrum, where the autism spectrum represents only one dimension among many. These findings highlight the complex nature of neuropsychiatric conditions, where genetic variations interact and accumulate to shape the observed behavioral phenotypes. By recognizing the shared genetic influences and overlapping features among neuropsychiatric conditions, we can move towards a more individualized approach to diagnosis and treatment. This approach would consider the specific gene variants and biological pathways involved in each person's presentation, and would facilitate tailored interventions that target the underlying mechanisms contributing to their specific symptoms. Embracing this concept would promote a shift from rigid disorder classifications to a more nuanced understanding that paves the way for personalized diagnosis, treatment, and ultimately a better appreciation of the underlying biology of these conditions.

Afterword

Completing this thesis has been an enlightening and rewarding journey into the exploration of shared genetic risk factors and underlying biological mechanisms linking ASD and ADHD, which revealed the importance of the identification and understanding of shared genetic

variations and their underlying biological mechanisms for the development of more effective treatments.

The field of research on ASD and ADHD is dynamic and ever-evolving, with a wealth of literature and freely accessible resources contributing to our knowledge base. The continuous stream of new discoveries in genetics, neuroscience, and clinical practice constantly shapes our understanding of these complex disorders. As such, this thesis serves as a response to the current advancements and developments in this field by emphasizing the importance of ongoing interdisciplinary collaborations and genetic sequencing to further expand our knowledge and understanding of these disorders.

As I conclude this thesis, I want to express my gratitude to the researchers, scientists, and organizations who have dedicated their time and efforts to research on ASD and ADHD. May our collective endeavors pave the way for a brighter future in understanding and accommodating the needs of individuals with neurodevelopmental disorders.

Appendix:

SFARI gene dataset:

https://docs.google.com/spreadsheets/d/e/2PACX-1vQ6EWpWtyEBc8BjrZucLhn7GOqA8T3_J9WqRIDyFwls4gAP5D7NxmWkEylGog9JgzQ9oaG77RbNO6w-/pubhtml

Original database source:

https://gene.sfari.org/database/human-gene/

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