# A Multimodal Approach toward the Biological Categorization of Autism

## Development of Theoretical Models, Classification Methods, and Biomarkers

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*To knowledge*

# ABSTRACT

Autism Spectrum Disorder (ASD) is an umbrella term for a group of neurodevelopmental disorders (NDD) which are behaviorally defined by the presence of difficulties with social communication, and behavioral rigidity and repetitiveness, including sensory disturbances. The overarching aim of this thesis was to improve the categorization of autism through the development of a theoretical framework and a multivariable classification method, and identify biomarkers which together would aid in the understanding of autism and be used in ASD classification.

*Paper I* presents a theoretical framework for the pathogenesis of ASD and other NDDs. The framework conceptualizes and operationalizes a three-factor model: (1) a *disorder personality type* that is specific for each NDD diagnostic category, but extends across the threshold for diagnosis and is not maladaptive in and of itself; (2) *cognitive capacity* as the ability of the individual to compensate for issues that may arise from of a "pronounced" personality type; (3) *neuropathological burden* which is conceptualized as the inhibition of neural and cognitive development resulting from the presence of neurodevelopmental risk factors. It is concluded that such a framework may contribute to an improved understanding of pathogenetic mechanisms underlying NDDs, including ASD.

Papers II-IV are based on a structural and functional brain imaging study of a group of adult males with ASD, and an age- and IQ-matched group of neurotypical controls. *Paper II* is a morphometric study that presents a multivariable classification method which showed up to 79% accuracy for diagnostic status, and which outperformed machine learning algorithms on the same dataset. *Paper III* investigated the source space magnetoencephalographic activation in the right fusiform gyrus in response to faces and face-like objects and found only late post-stimulus group differences, potentially relating to differences in top-down cognitive mechanisms. *Paper IV* compared the change in occipital magnetoencephalographic power in the gamma range in response to moving stimuli and showed a relationship with self-reported sensory sensitivity across both the ASD and control groups.

In summary, the thesis presents a theoretical framework that proposes pathogenetic mechanisms for ASD and other NDDs, a simple classification method for multivariable categorization using quantitative data, and biomarkers for face processing and sensory sensitivity.

**Keywords**: Autism, Classification, Biomarker, Theoretical Framework, Magnetoencephalography, Magnetic Resonance Imaging, Morphometry

# SAMMANFATTNING PÅ SVENSKA

Autism är ett paraplybegrepp för en grupp utvecklingsneurologiska tillstånd som beteendemässigt karakteriseras av svårigheter med social kommunikation, repetitiva och rigida beteendemönster, inklusive sensoriska avvikelser. Det huvudsakliga syftet med detta avhandlingsarbete var att utveckla metoder för att förbättra diagnostiken av autism, vilket inkluderar utveckling av ett teoretiskt ramverk och en statistisk metod för multivariabel klassifikation, samt identifikation av biologiska markörer som kan användas för att förbättra förståelsen av autism och användas i det diagnostiska arbetet.

*Artikel I* presenterar ett teoretiskt ramverk för hur autism och andra neuropsykiatriska funktionsnedsättningar uppstår. Ramverket konceptualiserar och operationaliserar en trefaktormodell: (1) en *tillståndsrelaterad personlighetstyp* som är specifik för varje diagnos, men sträcker sig över den diagnostiska tröskeln och i sig inte är patologisk; (2) *kognitiv kapacitet* som är individens förmåga att kompensera för svårigheterna som uppstår vid uttalade personlighetsdrag; (3) *neuropatologisk belastning* som representerar den negativa påverkan på hjärnan och den kognitiva utvecklingen som blir resultatet när individen utsätts för utvecklingsneurologiska riskfaktorer. Implikationen av ramverket är en förbättrad förståelse för de patogenetiska mekanismer som bidrar till att neuropsykiatriska funktionsnedsättningar, inklusive autism, utvecklas.

Artiklarna II-IV baseras på en strukturell och funktionell hjärnavbildningsstudie som inkluderar en autism-kontroll-kohort med ålders- och IQ-matchade vuxna män. *Artikel II* rapporterar om en morfometrisk studie som presenterar en statistisk metod för multivariabel klassifikation som visade sig vara upp till 79% träffsäker för diagnostisk status och överträffade maskininlärningsalgoritmer när dessa testades på samma data. I *artikel III* undersöktes magnetencefalografisk aktivering i hjärnans höger fusiforma gyrus vid presentation av ansikten och ansiktsliknande objekt och man fann endast sena gruppskillnader efter stimuluspresentation, vilket kan relatera till skillnader i top-down kognitiva mekanismer. I *artikel IV* jämfördes skillnader mellan grupperna i occipital magnetencefalografisk power i gamma-omfånget som reaktion på rörliga visuella stimuli och man påvisade ett samband med självskattad sensorisk känslighet i både autism- och kontrollgruppen.

Sammanfattningsvis presenterar avhandlingsarbetet ett teoretiskt ramverk vilket föreslår patogenetiska mekanismer för autism och andra neuropsykiatriska funktionsnedsättningar, en enkel klassifikationsmetod för multivariabel kategorisering utifrån kvantitativa data, och biomarkörer för ansiktsbearbetning och sensorisk känslighet.

# SAŽETAK NA SRPSKOM

Poremećaj autističnog spektra je krovni termin za grupu bolesti koji se karakterišu bihejvioralno po smetnjama socijalne komunikacije, repetitivnih i rigidnih ponašanja, i senzornih smetnji. Glavni cilj ove doktorske teze je razvoj metoda za poboljšanje klasifikacije autizma, koji uključuje razvoj teoretskog modela i statističke metode za multivariabilnu klasifikaciju, kao i identifikacija bioloških markera u cilju poboljšanja razumevanja autizma i korišćenja u njenoj klasifikaciji.

*Rad I* prezentuje teoretski okvir za nastanak autizma i drugih neurorazvojnih poremećaja. Okvir konceptualizuje i operacionalizuje trofaktoni model: (1) *tip ličnosti vezan za pojedine dijagnoze* koji je specifičan za tu dijagnozu, ali se proteže preko dijagnostičkog praga i nije sam po sebi patološki; (2) *kognitivni kapacitet* koji označava kapacitet osobe da kompenzuje smetnje koje nastaju pri izraženom ličnošću; (3) *neuropatološki teret* koji dovodi do inhibicije razvoja mozga i kognitivnih sposobnosti prilikom izloženju neurorazvojnim rizičnim faktorima. Implikacija ovog okvira je poboljšanje razumevanja patogenetskih mehanizmi koji doprinose razvoju neurorazvojnim poremećajima.

Radovi II-IV se osnivaju na neuroradiološkoj i neurofizioloskoj studiji na uzorku autizam-kontrola gde se grupe sastoje od odraslih osoba muškog pola izjednačenih uzrasta i nivoa inteligencije. *Rad II* je morfometrijska studija koja prezentuje statističku metodu za multivariabilnu klasifikaciju koja je bila do 79% tačna za diagnostički status i nadmašila je algoritme mašinskog učenja kada su testirani na istim podacima. *Rad III* ispitivao je magnetoencefalografnu aktivaciju u desnom fusiformnom režnju pri prezentaciji lica i pareidolskih objekata i pronađene su samo grupne razlike u kasnom post-stimulusnom periodu, koje mogu odgovarati razlikama top-down kognitivnih mehanizmi. *Rad IV* uporedio je promene u okcipitalnom magnetoencefalografnom power-u u rasponu gamma talasa kao reakcija na pokretljive vizualne stimuluse, koje je pokazalo da postoji odnos sa samoprijavljenim senzornim smetnjama u autističnoj, kao i u kontrolnoj grupi.

Ukratko, ova doktorska teza prezentuje teoretski okvir koji predlaže patogenetske mehanizme za nastanak autizma i drugih neurorazvojnih poremećaja, prostu klasifikacionu metodu za multivariabilnu kategorizaciju pomoću kvantitativnih podataka, i biološke markere za tumačenje lica i senzornu osetljivost.

# LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. **Sarovic D**. A framework for neurodevelopmental disorders: Operationalization of a pathogenetic triad.
Preprint published on PsyArXiv 2019.
Doi:10.31234/osf.io/mbeqh

II. **Sarovic D**, Hadjikhani N, Schneiderman JF, Lundström S, Gillberg C. Autism classified by magnetic resonance imaging: A pilot study of a potential diagnostic tool.
International Journal of Methods in Psychiatric Research, 2020; e1846.
Doi:10.1002/mpr.1846

III. **Sarovic D**, Hadjikhani N, Schneiderman JF, Lundström S, Riaz B, Orekhova E, Khan S, Gillberg C. Pareidolia as a probe for early and late face processing components in autism: A magnetoencephalographic study.
(Under review)

IV. Orekhova, EV, Stroganova, TA, Schneiderman, JF, Lundström, S, Riaz, B, **Sarovic**, **D**, Sysoeva, OV, Brant, G, Gillberg, C, Hadjikhani, N. Neural gain control measured through cortical gamma oscillations is associated with sensory sensitivity.
Human Brain Mapping 2018; 1–11.
Doi:10.1002/hbm.24469

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AASP | Adolescent/Adult Sensory Profile |
| ALT | Autistic-Like Trait |
| ANOVA | Analyses of Variance |
| AQ | Autism Spectrum Quotient |
| BAP | Broader Autism Phenotype |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EEG | Electroencephalography |
| E/I | Excitation/Inhibition |
| ERF | Event-Related Field |
| F | Face (stimulus type) |
| FFA | Fusiform Face Area |
| FLO | Face-Like Object (stimulus type) |
| GNC | Gillberg Neuropsychiatry Centre |
| GSS | Gamma Suppression Slope |
| HB | Holm-Bonferroni |
| HPI | Head Position Indicator |
| HRV | Heart Rate Variability |
| ICA | Independent Component Analysis |
| IQ | Intelligence Quotient |
| LOOCV | Leave-One-Out Cross-Validation |
| MDE | Multidisciplinary Neuropsychiatric Evaluation |
| MEG | Magnetoencephalography |
| MNE | Minimum Norm Estimate |
| MRI | Magnetic Resonance Imaging |
| MSR | Magnetically Shielded Room |
| NB/CC | Neuropathological Burden/Cognitive Capacity |
| NDD | Neurodevelopmental Disorder |
| O | Object (stimulus type) |
| ROI | Region of Interest |
| TI | Total Index |
| UAR | Unweighted Average Recall |
| WAIS | Wechsler Adult Intelligence Scale |
| WISC | Wechsler Intelligence Scale for Children |

# DEFINITIONS IN SHORT

| | |
|---|---|
| Descriptive semantics | The identity-first nomenclature ("autistic individual") will be used because it is less cumbersome (than "individual with autism") and more often preferred by the autistic community. There is disagreement which terminology to use. This thesis makes no attempt to enter the discussion, and acknowledges that the terms refer to the same abstraction, and can be used interchangeably according to the reader's preference. |
| Biological hierarchy | The association between mechanisms that are physiologically coupled across biological levels: Genetic architecture → Neurobiological endophenotype → Neuropsychological phenotype → Behavioral phenotype. |
| Biomarker | Short for "biological marker", which is a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathogenic process, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working, 2001). |
| NB/CC-complex | The joint effect of the neuropathological burden and cognitive capacity, due to their intricate relationship in modulating brain development and influencing clinical ascertainment. |

# 1 INTRODUCTION

Autism has gone from being thought of as an exceedingly rare disorder with very severe disability, to being recognized as a common condition with varying degrees of disability. There are several reasons for this, such as an increased awareness, recognition of its existence in individuals with lower degrees of disability, and an improved identification of such individuals. Autism is identified through clinical interviews and neuropsychological testing, and although this approach is well established, it has specific drawbacks, partly due to intrinsic properties of autism, and partly due to our lack of understanding of it.

The recognition of it being a common disorder has attracted the interest of both the general public and researchers. Although the scientific literature has been successful in characterizing many aspects of the condition, there is no single agreed upon framework, and there are fervent discussions regarding the nature of autism (Eigsti & Fein, 2022; Levy, 2022; Lombardo & Mandelli, 2022). This has given rise to difficulties explaining some observed patterns and making empirical predictions, as well as limited the detection of autism in individuals where the clinical interview has low sensitivity. This thesis will argue that the lack of a theoretical framework outlining causative mechanisms represents a major obstacle to the academic inquiry of autism, and that there is a need to develop methods for its identification that are grounded in contributory mechanisms.

One such approach is to rely on biological features, in addition to subjective interviews. The development of classification methods that are guided by valid biological frameworks may increase the sensitivity for under-diagnosed groups, such as females (Eberhard, Billstedt, & Gillberg, 2022) and those with high cognitive ability. Because the decreased sensitivity for these groups stems from phenotypic compensation, biological methods for detection do not share this limitation. The low sensitivity for these groups delays diagnoses (Bargiela, Steward, & Mandy, 2016; Begeer et al., 2013; Geurts & Jansen, 2012; Goin-Kochel, Mackintosh, & Myers, 2006) and leads to development of secondary mental health issues (Belcher, Stagg, & Ford, 2016); improving their detection would lead to better outcomes.

I will first provide the context for this work by outlining aspects in the scientific literature that are relevant to its aims. After that, the methods will be outlined, with emphasis on the patient-control cohort in papers II-IV. Following this, the main results and findings for each paper will be presented, followed by a discussion. Finally, main conclusions and future directions will be presented, including implications for clinical practice and research.

# 1.1 AUTISM SPECTRUM DISORDER

Autism was previously thought to be an extremely rare disorder, but has in recent decades been identified as being relatively common, with a prevalence of around 1% (Zeidan et al., 2022). This increase is due to several factors, including diagnostic substitution (Coo et al., 2008), increased awareness among clinicians and researchers (Elsabbagh et al., 2012; Rice et al., 2012), and a gradual decline in the intensity of the phenotype required to receive a diagnosis (Arvidsson, Gillberg, Lichtenstein, & Lundstrom, 2018). There is, however, little to suggest that the actual rate of autism and autistic-like traits (ALTs) in the population has increased over the same time period (Lundstrom, Reichenberg, Anckarsater, Lichtenstein, & Gillberg, 2015).

What was previously thought to occur solely due to environmental factors (erroneously, the influence of parenting behaviors) has been recognized as developing due to a combination of environmental (including biological and psychosocial risk factors) and genetic effects (Lai, Lombardo, & Baron-Cohen, 2014; Taylor et al., 2020). For an exposé on the history of autism, see Coleman & Gillberg (2012).

## 1.1.1 SYMPTOMS AND DESCRIPTION

According to the Diagnostic and Statistical Manual of Mental Disorder-5 (DSM-5; (American Psychiatric Association, 2013)), autism is a collective term for a group of conditions that are defined by the presence of deficits in social communication and interaction, as well as restricted and repetitive behaviors, including sensory alterations, that are present from early childhood and cause significant impairment of functioning (see Table 1 for diagnostic criteria). These alterations may present themselves differently in different individuals, with varying degrees of intensity. The overall severity of the impairment is denoted using three levels that indicate the amount of support needed (from "requiring support" to "requiring very substantial support"). Autism is furthermore specified regarding the presence of accompanying intellectual or language impairment, another neuropsychological disorder (neurodevelopmental, mental, or behavioral), catatonia, a known medical or genetic condition, or a contributing environmental factor.

*Table 1. Diagnostic criteria for autism spectrum disorder according to the DSM-5*

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

(1) Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

(2) Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

(3) Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

(1) Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

(2) Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).

(3) Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).

(4) Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

### 1.1.2 DIAGNOSTIC PROCEDURE

Autism is a behaviorally defined condition, and there is currently no biological test that can diagnose it with adequate accuracy. The gold standard procedure for the identification and evaluation of autism is the use of a multidisciplinary neuropsychiatric evaluation (MDE; (Falkmer, Anderson, Falkmer, & Horlin, 2013; Kaufman, 2020). MDEs are performed by multiple professionals (psychiatrists, clinical psychologists, speech pathologists), and usually involve anamnesis (with the patient, parents, school teachers, including a review of the medical journals), observation (clinically, in school, at home), somatic and genetic examinations, and neuropsychological assessments (intelligence, executive functions). Through the wide scope of the evaluation, one is able to identify whether the individual fulfills the diagnostic criteria, if there are associated conditions or contributing factors, and how severe the impairment is, including the amount and type of support needed.

The evaluation process is both costly and time consuming, which has contributed to long waiting times for evaluation following referral to psychiatric clinics (Bisgaier, Levinson, Cutts, & Rhodes, 2011). For example, at two subspecialized neuropsychiatric child and adolescent psychiatry clinics in Sweden, the total time to perform a complete evaluation is 15–30 hours, and costs 30–60'000 Swedish krona, with the time from referral until completion of the evaluation being 1–1.5 year (L. Brännvall, personal communication, February 16, 2022; U. Ferm, personal communication March 13, 2022). To mitigate this issue, one must not only educate and employ many more mental health professionals, but also develop more scalable methods for identification.

The actual accuracy of the MDE is important to elucidate since the diagnostic accuracy of any instrument or classification method is compared with that of the current best practice. The optimal method is for several multidisciplinary teams to blindly diagnose the same set of individuals, and compare their inter-rater reliability[1], but no such studies exist. In the absence of such studies, any other approach for estimating the true accuracy will have methodological constraints.

Some studies have investigated inter-rater agreements between the assessments of individual clinicians (Gillberg et al., 1990; Lord, 1995; Lord et al., 2006; Stone et al., 1999; van Daalen et al., 2009), with agreements ranging from 87% to 100% for an autism spectrum diagnosis (however, all included children under the age of

[1] Inter-rater reliability is tested and maintained for administration of the Autism Diagnostic Observation Schedule-2. The trainee is required to show an agreement of at least 80% with the trainer or clinic. However, the evaluations of the trainer are considered accurate, eluding an estimation of the baseline accuracy for the method itself.

three). When excluding assessments that were potentially confounded by the evaluators either basing their diagnosis on the same clinical information, or having access to past medical and treatment histories (i.e. not blinded evaluations, as when a patient is first referred for an evaluation), the accuracy ranges were 88-90% for an autism spectrum diagnosis, and 64-76% for individual diagnoses under the autism spectrum umbrella ((Lord et al., 2006; Stone et al., 1999); these were also the studies with the largest sample sizes). It should be noted that the clinicians in Lord et al. (2006) actively maintained a high inter-rater reliability through joint monthly assessments on cases outside the study. Given that this is not employed within all clinics, and certainly not feasible between clinics, their accuracy of 90% is inflated when compared with accuracies on a national or global level. These studies together indicate that the accuracy of blinded single-clinician evaluations is likely below 90%.

Another approach that has been used is through the assumption that the presence of autism is stable over time. Even though an individual may present with more or less impairment at a given time, the underlying issues and phenotype are expected to be stable across a lifetime (Billstedt, Gillberg, & Gillberg, 2007; Holmboe et al., 2014; Lundstrom et al., 2015). By assessing individuals at different timepoints, one can compare the diagnostic stability, where an instability represents inaccuracy in the evaluation process given the previous assumption. Although there are clear limitations (with interventions and age-related improvement underlying part of the diagnostic instability), this approach has indicated that the classification accuracy for autism and autism spectrum disorder are at most 90% and 80% respectively (Falkmer et al., 2013; Woolfenden, Sarkozy, Ridley, & Williams, 2012), with Falkmer et al. (2013) suggesting that an accuracy above 80% should be considered equal to the current best practice.

Since the assessment of symptom criteria and the level of clinical impairment are inherently subjective and may be moderated by both clinician perception (such as from other referrals) and the individual's current psychosocial situation and cognitive demands, there can be no universal and objective diagnostic threshold. For this reason, threshold cases will inevitably spur disagreement, and the empirical accuracy of a hypothetically perfect gold standard method can never reach 100%. Given the studies outlined above, and considering that multidisciplinary teams may have greater agreement than single-clinician evaluations (although this can be argued; (Kaufman, 2020)), one may expect the gold standard accuracy for the autism spectrum disorder umbrella to be close to 90%, and likely below 80% for individual diagnoses under the umbrella. These represent the benchmark values that classification studies should be compared against.

### 1.1.3 CONUNDRUMS IN THE LITERATURE

There are features of autism that have impeded its academic and clinical characterization, necessitating explanations and further study. One such issue is that of heterogeneity (Jeste & Geschwind, 2014; Molloy & Gallagher, 2021). Although autism is far from the only condition that is biologically and clinically heterogeneous, it is a particularly intense topic of discussion in this field. Both behaviorally and biologically, there is a high degree of variability between individuals, and there are efforts to develop approaches for stratification in order to identify homogeneous subgroups. There are several potential reasons for this heterogeneity. It may be because one is studying various phenomena that are not a single condition at all; the conditions may lack biological connections but present with a similar behavioral phenotype. This would imply a low validity for autism as a singular entity (at least biologically) which has been argued by Waterhouse et al. (2016). Another possibility is that the heterogeneity is intrinsically coupled to the autistic condition; an inextricable fact where the path toward personalized medicine and improved therapeutic interventions necessitates improved stratification of relevant subgroups (Molloy & Gallagher, 2021; Mottron & Bzdok, 2020).

A third possibility is that it is due to the lack of a framework and therefore the understanding of underlying mechanisms, which this thesis, and paper I in particular, will argue. The lack of a framework poses a circular problem, in which the heterogeneity makes the underlying mechanisms less discernible, and the lack of a defined model contributes to the perceived heterogeneity. It may be that the identification of the mechanisms that contribute to heterogeneity allows one to parse out their effects, leaving a homogenized phenotype. This is postulated in paper I, and some of its predictions, such as increased heterogeneity in samples with lower cognitive ability, are empirically testable.

Another feature that has been difficult to explain is that there are sex differences, both with regard to prevalence rates (more common in males) and biological and behavioral phenotypes. Theories, such as autism being associated with masculinization (Baron-Cohen, 2002), have been developed to explain the difference in prevalence. However, the idea that males are more susceptible (due to higher testosterone) has been difficult to reconcile with the finding that autistic females have a higher disease burden, termed the female protective effect (Gockley et al., 2015; Robinson, Lichtenstein, Anckarsater, Happe, & Ronald, 2013). For example, females with similar degrees of impairment as males tend to have lower cognitive ability (Dworzynski, Ronald, Bolton, & Happe, 2012; Rivet & Matson, 2011; Van Wijngaarden-Cremers et al., 2014), implying that they carry

more deleterious genetic variants and/or have an increased exposure to environmental risk factors.

What has proved most difficult to explain is that some autistics and their relatives have cognitive strengths (Baron-Cohen, Ashwin, Ashwin, Tavassoli, & Chakrabarti, 2009; Baron-Cohen, Wheelwright, Burtenshaw, & Hobson, 2007; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; Wheelwright & Baron-Cohen, 2001) and that the common genetic variants that underlie autism are positively associated with high intelligence and educational attainment (Clarke et al., 2016; Weiner et al., 2017). This is counterintuitive since autism is associated with a decreased average cognitive ability and educational attainment, and requires an explanation. Existing theories have attempted to incorporate this finding. For example, the extreme male brain theory (Baron-Cohen, 2002) and its effect on cognitive styles termed systemizing and empathizing (Baron-Cohen, 2009) may predict an improved intuitive understanding of physics and engineering, and therefore increase the educational attainment in STEM-related areas (science, technology, engineering, mathematics). However, the increases in general intelligence and educational attainment should be associated with performance not just in STEM-related fields. A weak central coherence (Frith, 1989) may predict an increased ability for bottom-up perception and information processing, but the effects on top-down cognition will have increasingly negative effects with increasing educational level, and give lower, or at least uneven, scores for general intelligence and executive function. The intense world theory (H. Markram, Rinaldi, & Markram, 2007; K. Markram & Markram, 2010) predicts that autistics have hyper-processing, hyper-memory, and so on, due to increased activity in neural networks and sensitivity to stimuli, which extends to an improved cognitive ability. That may be true for simple and linear processes (such as increased visual acuity and improved vision in low-light settings with larger eyes, or increased strength with larger muscle mass), but will not hold true for complex and non-linear processes such as intelligence and educational attainment, which are instead dependent on an intricate coordination requiring both increased and decreased activity, even within each neural network, depending on the task.

The presented issues may be solved with a theoretical framework that integrates these findings through mechanisms that span the biological hierarchy and relates them to the autistic phenotype.

### 1.1.4 ETIOLOGICAL FACTORS

The etiology of autism is both heterogeneous and complex, with contributions from nature as well as nurture. Twin studies indicate a very high heritability (Sandin et al., 2017; Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016), and a wide

range of contributing risk factors have been identified that include both endogenous and exogenous mechanisms (Modabbernia, Velthorst, & Reichenberg, 2017). The following chapters will briefly outline the contributions from genetic and environmental factors.

### 1.1.5 GENETIC FACTORS

The heritability of autism has been estimated to range between 64% and 91% (Sandin et al., 2014). It is modulated by cognitive ability, such that a lower intelligence quotient (IQ) is associated with lower heritability (Xie et al., 2020). The genetic architecture is complex, with both monogenic and polygenic models having been proposed and studied. Genome-wide association studies have identified thousands of low-risk loci (Autism Spectrum Disorders Working Group of The Psychiatric Genomics, 2017; Gaugler et al., 2014), so called common variants. These have been used to calculate polygenic scores for autism (Grove et al., 2019; Robinson et al., 2016), which dose-dependently influence the probability of an autism diagnosis (Grove et al., 2019; Weiner et al., 2017). For example, the polygenic score for autism in close relatives predicts the severity of the autism in the proband. They have also been found to correlate positively with IQ and educational attainment (Brainstorm et al., 2018; Clarke et al., 2016; Crespi, 2016; Grove et al., 2019; Weiner et al., 2017), and have been found to be involved in the regulation of synaptic function and activity (Bourgeron, 2015), likely relating to the neuroanatomical and neurophysiological alterations identified in the literature.

Rare, high-risk variants have also been found to contribute to the risk of autism, and are found at an increased rate in autism compared with undiagnosed individuals (Girirajan et al., 2012; Pizzo et al., 2019). They are associated with negative effects on cognitive development (Chawner et al., 2019; Robinson et al., 2016), and show both heterogeneity within the autism group and overlap with other neurodevelopmental disorders (NDD; (Chawner et al., 2019; Cross-Disorder Group of the Psychiatric Genomics, 2019; Khanzada, Butler, & Manzardo, 2017)). They are increasingly common with higher parental age, possibly explaining why advanced parental age is a risk factor (Hehir-Kwa et al., 2011; Wu et al., 2017). The effects of common and rare variants are additive with regard to risk of autism (Weiner et al., 2017).

Multiple genetic syndromes, such as Down's, Rett's, and Fragile X, have an increased rate of co-occurring autism (Moss & Howlin, 2009). These genetic syndromes are often associated with decreased cognitive ability, and it may be that cognitive ability modulates their clinical overlap, similar to that of highly penetrant rare variants. Genomic imprinting (for overview, see (Tucci, Isles, Kelsey, Ferguson-Smith, & Erice Imprinting, 2019)) has also been implicated in the

development of autism (Li et al., 2020). As an example, females with Turner syndrome (possessing only one X-chromosome) may show differences in social cognition and executive function depending on which parent the X-chromosome originates from (Skuse, 2000; Skuse et al., 1997).

### 1.1.6 ENVIRONMENTAL FACTORS

Although there is a strong genetic component, the risk of developing autism is increased through the contribution of a wide range of environmental factors which span from the pre- to the postnatal period (for meta-reviews see (Kim et al., 2019; Modabbernia et al., 2017)). Parental age is positively related to risk (Wu et al., 2017), likely due to the accumulation of rare variants. Pregnancy-related infections and maternal autoimmune disease have been shown to increase risk (H. Y. Jiang et al., 2016; Tioleco et al., 2021), possibly as a secondary effect due to maternal immune activation (Brucato et al., 2017; Chen et al., 2016; Croen et al., 2019). Toxins and medications, such as inorganic mercury, anti-epileptics and antidepressants, have also been found to increase risk (Boukhris, Sheehy, Mottron, & Berard, 2016; Christensen et al., 2013; Yoshimasu, Kiyohara, Takemura, & Nakai, 2014), as have pre- and perinatal complications (Gardener, Spiegelman, & Buka, 2009, 2011) and vitamin deficiencies (Fernell et al., 2015).

Most, if not all, of these risk factors have been found to both increase the risk of other NDDs, and to negatively affect neurodevelopment and cognitive ability in the neurotypical population (see table 2 and supplementary material in paper I). In other words, their neurodevelopmental effects are not specific for autism. Far from all individuals with autism have a clearly identifiable risk factor, and the types of risk factors present are highly heterogeneous, with each risk factor being identifiable only in small subsets of individuals. This indicates that there is not one singular cause of autism, and studies that proclaim they have found such a thing should be met with skepticism. This, together with the fact that the risk factors are non-specific for any NDDs speak in favor of them affecting a modulating variable, rather than the core disease mechanisms.

### 1.1.7 PHENOTYPES

Studies investigating autism have identified myriad potential differences, including both biological and behavioral, ranging from genetic and neurobiological to somatic and cognitive (Frye et al., 2019; Loth et al., 2021). These phenotypes vary, both with regard to their strength in differentiating case-control groups (individual effect sizes), as well as with how common they are in autistic individuals (prevalences). No single phenotype has yet been identified with a large enough effect size (Loth et al., 2021) or in a large enough majority of autistics to be used for classification (Molloy & Gallagher, 2021), which is why

the use of multivariable methods are necessary. By determining the generalizability of effect sizes and prevalence rates for such biomarkers, one may develop more informed multivariable classification methods.

When studying "autistic phenotypes", one should always consider how each phenotype arises and contributes to the development of autism, since they may develop in other neurodevelopmental and psychiatric conditions as well, such as due to the effects of shared genetic or environmental risk factors. Also, it is important to integrate the phenotypes vertically and horizontally across the biological hierarchy in order to understand how one phenotype may affect another. As an example, brain connectivity studies find both increased and decreased short-range connectivity (two-tailed findings; (Paakki et al., 2010; Vissers, Cohen, & Geurts, 2012)), but may show only increased or decreased connectivity (one-tailed findings) if stratified for subsamples with and without subclinical epileptic activity, since the increased baseline neural activity may affect the ratio of synaptic budding and pruning with secondary effects on neural network topology. Lack of control for such physiological interaction effects is likely at least one of the contributors to the heterogeneity of the autism literature.

For practical reasons, many of the studies investigating a specific phenotype, in particular those that focus on the neurobiological endophenotype, have small sample sizes and fail to investigate its specificity by including other NDDs for comparison. Bearing in mind that phenotypes may be nonspecific for autism, I will mention some of those that have been presented in the literature.

### 1.1.8 NEUROBIOLOGICAL ENDOPHENOTYPE

The neurobiological endophenotype can be grossly categorized into structural and functional components. The specific neurobiological endophenotypes identified in the autism literature may seem disparate, such as patterns of synaptic budding and pruning, epileptic and subthreshold neural activity, excitation/inhibition balance, and connectivity patterns. However, many of them interact and can be physiologically coupled to common global functional mechanisms. At the end of this section, I will make an effort to integrate them into a physiological framework. Hopefully this conceptualization may aid in the planning of future studies that aim to integrate several of these mechanisms, since the empirical evidence for their integration is still weak, as each endophenotype is mostly studied in isolation.

One of the earliest identified and most studied is that of increased head circumference and brain size during early childhood (Courchesne, 2002; Sacco, Gabriele, & Persico, 2015). It is notable that there is an interaction with cognitive ability (Yankowitz et al., 2020), and that the increase in size becomes more

prevalent with decreasing cognitive ability (Sacco et al., 2015), indicating that it may result from an interaction with mechanisms underlying low cognitive ability. Individual brain regions, ranging from parts of the cerebral cortex to the cerebellum and limbic system, have been found to differ not only with regard to macroscopic features (such as volume and shape), but also microscopically (such as differences in Purkinje and parvalbumin neurons, and structural alterations of minicolumns) (Donovan & Basson, 2017; Ecker, 2017; Ecker, Schmeisser, Loth, & Murphy, 2017; Fischi-Gomez, Bonnier, Ward, Granziera, & Hadjikhani, 2021).

Studies investigating brain connectivity have found decreased white matter integrity (which can predict symptom severity; (Vissers et al., 2012)) and alterations in the patterns of connectivity between different areas (with variable degrees of replicability, as noted above (King et al., 2019)). For example, studies using functional magnetic resonance imaging (MRI) have identified decreased fronto-parietal (Vissers et al., 2012), homotopic, and cortico-striatal connectivity (King et al., 2019). For neurophysiological methods with higher temporal resolution (such as electroencephalography (EEG) and magnetoencephalography (MEG)), the findings are more heterogeneous, possibly due to differences in analyzed frequency bands and sample characteristics. However, long-range (and possibly also short-range) functional connectivity seems to be decreased, and there is abnormal lateralization (Khan et al., 2015; O'Reilly, Lewis, & Elsabbagh, 2017).

It has been proposed that an altered ratio between excitation and inhibition (E/I-ratio) in the brain is central to the development of autism (Hussman, 2001; Rubenstein & Merzenich, 2003; Uzunova, Pallanti, & Hollander, 2016), and multiple studies have found alterations in the neural systems underlying cortical excitation and inhibition (Bruining et al., 2020; Canitano & Palumbi, 2021). This could explain the increased rates of epilepsy and epileptic activity, and some of the behavioral alterations seen with manipulation of the E/I-ratio pharmacologically (Canitano & Palumbi, 2021). Although there is no consensus regarding which individual measure best estimates the E/I-ratio in vivo (Cousijn et al., 2014; Perry, Brindley, Muthukumaraswamy, Singh, & Hamandi, 2014), stimulus-induced neural oscillations in the gamma range (>30 Hz), which arise from an intricate interaction between excitatory and inhibitory neuron populations (Buzsaki, 2006; Buzsaki & Wang, 2012), have shown promise (Levin & Nelson, 2015; Nelson & Valakh, 2015). In light of this, alterations in the gamma range have been identified in autistics and their relatives (Khan et al., 2015; Kitzbichler et al., 2015; Orekhova et al., 2007; Rojas, Maharajh, Teale, & Rogers, 2008). The association between gamma oscillations and sensory processing (Rossiter, Worthen, Witton, Hall, & Furlong, 2013; Sedley & Cunningham, 2013) may imply that an alteration in one translates to the other.

A key cortical area when it comes to face processing is a part of the fusiform gyrus known as the Fusiform Face Area (FFA), which is located on the inferior temporal cortex. There have been findings of both normal (Feuerriegel, Churches, Hofmann, & Keage, 2015) and abnormal (Bailey, Braeutigam, Jousmaki, & Swithenby, 2005; McPartland, Dawson, Webb, Panagiotides, & Carver, 2004) signatures in the FFA in autistic individuals. In light of connectivity findings (relatively decreased long-range compared with short-range connectivity) and neuropsychological frameworks (such as weak central coherence), it has been proposed that face processing includes a reliance on the bottom-up processing of low-level features rather than top-down holistic processing (Dawson, Webb, & McPartland, 2005; Jemel, Mottron, & Dawson, 2006). Concretely, this would imply that autistics have an intact recognition of first-order configuration of faces (identifying a face as being a face through universal features such as two eyes, above a nose, above a mouth; (Diamond & Carey, 1986)), but could have difficulty with the identification of individual faces, and more so facial expressions, due to non-universal differences in facial configurations (second-order configuration, such as the shapes, sizes, and relative distances between facial features). Studies using EEG and MEG have shown that pareidolic face-like objects (such as smileys, and sometimes the fronts of cars or electrical outlets), which have the same first-order configuration as faces, elicit similar cortical activity as when presented with real faces (Caharel et al., 2013; Churches, Baron-Cohen, & Ring, 2009; Hadjikhani, Kveraga, Naik, & Ahlfors, 2009; Maurer, Grand, & Mondloch, 2002).

We can attempt to conceptualize the findings regarding genetic architecture, neurobiological endophenotype, and risk factors, and the effect they have on the behavioral and cognitive phenotypes. Remembering that there is a positive correlation between common genetic variants for autism and cognitive ability, and that many of those variants are involved in synaptic function, it is possible that the genetic susceptibility for autism is associated with increased rates of neurite and synapse generation (for review see (Gilbert & Man, 2017)), which increases the computational capacity of neural networks. However, an increased number of synapses comes at a cost, since they require both energy and space, with further increases instead lowering energy efficiency and leading to suboptimal network topologies. In other words, the ratio of synaptic budding/pruning shows an inverted U-curve with respect to network efficiency. To achieve optimality, neural networks eliminate unnecessary synapses and neurites depending on input and network activation patterns (Chechik, Meilijson, & Ruppin, 1998; Navlakha, Barth, & Bar-Joseph, 2015; Scholl, Rule, & Hennig, 2021). Suboptimal budding and pruning at the endophenotypic level may therefore lead to inefficiencies in network topologies, which may contribute to low cognitive ability and an increased rate of diagnoses at the phenotypic level. The effect of inefficient

network topologies would be particularly evident for higher cognitive functions, such as executive functions, that are more dependent on an intricate coordination between different brain areas and larger neural networks.

Synaptogenesis initiates before that of pruning, with most of the generation occurring prenatally, and the elimination postnatally, as neural networks receive input and operate on that information. If a core susceptibility for autism comes in the form of increased synaptogenesis, and the presence of an environmental risk factor inhibits neural physiology (more likely, since synapse elimination is an active process (Chung & Barres, 2012)), the budding/pruning-ratio may increase, leading to larger network and brain sizes. The ratio would likely further increase in the presence of epileptic activity. The first years of life are associated with massive reorganization at the cellular level, potentially explaining why autistic symptoms develop during these years (Ozonoff et al., 2018), and why regressive autism (or other induced NDDs), which has been associated with a larger brain size (Nordahl et al., 2011), can occur following exposure to a risk factor (Pearson, Charman, Happe, Bolton, & McEwen, 2018). This physiological framework would explain the association between macrocephaly and low cognitive ability in autistics, and the increased prevalence of environmental risk factors with effects on neurophysiology in clinical samples.

### 1.1.9 SOMATIC ENDOPHENOTYPE

Despite autism being a brain-related condition, evident through the neurobiological alterations outlined above, there are also multiple somatic alterations associated with the condition. Given their increased physiological distance from the brain, their roles in the development of autism are less specific. This implies that they are more sensitive as biomarkers for dysregulated neurodevelopment in general, and therefore as risk factors for NDDs as a group. This is illustrated by somatic endophenotypes (such as inflammation; (Han et al., 2021)) more often being shared among the disorders compared with neurobiological endophenotypes.

Immune activation, which occurs in response to infections or in autoimmune diseases, causes an inflammatory response in the body that may have secondary effects on the brain and its development. Alterations of immune function are a frequent finding in autistics (see reviews by (Han et al., 2021; Hughes, Mills Ko, Rose, & Ashwood, 2018; Robinson-Agramonte et al., 2022; Zawadzka, Cieslik, & Adamczyk, 2021)). Maternal immune activation during pregnancy has been used as an animal model for autism, and its effects have been identified in human studies as well. Autoimmune disorders are more common in mothers, probands and first-degree relatives of individuals with autism than the population in general. Furthermore, infections and fever during pregnancy have been shown to increase

risk (Shuid et al., 2021; Zerbo et al., 2013). The inflammatory response involves an increased production and circulation of inflammatory proteins, such as cytokines, which can cross the blood-brain barrier and negatively affect neurodevelopment (Goines & Ashwood, 2013; N. M. Jiang, Cowan, Moonah, & Petri, 2018).

Another frequent finding is that of autonomic dysfunction. The autonomic system is one of the body's main systems for maintaining homeostasis. As such, it plays a vital role in development and for optimizing physiological responses to environmental demands. Studies have found abnormal pupillary responses, galvanic skin responses, and heart rate variability, both during tasks and at rest (Arora, Bellato, Ropar, Hollis, & Groom, 2021).

Increased levels of heavy metals and other toxins have also been found in biological samples (Chun, Leung, Wen, McDonald, & Shin, 2020; Dutheil et al., 2021; J. Zhang et al., 2021). In some cases, this may be indicative of previous exposure (as an exogenous risk factor), and in others of abnormal metabolic function and excretion (as an endogenous risk factor). There are also frequent reports of dysregulation of the microbiome in autism; perhaps unsurprising given the growing understanding of the importance of the gut microbiome for the development and function of the brain (Saurman, Margolis, & Luna, 2020).

### 1.1.10 NEUROPSYCHOLOGICAL AND BEHAVIORAL PHENOTYPE

ALTs are behaviors that are similar to that of the autistic symptoms, but their presence does not necessitate a diagnosis of autism, since everyone possesses them to some degree (Ruzich et al., 2015). The more of them that an individual has, the more autistic they will seem, and the greater the probability that they will have a diagnosis (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). Studies have shown that ALTs and the clinical syndrome are underpinned by the same biological mechanisms and thus part of the same continuum, with diagnosed individuals being over-represented in the upper part of the spectrum (Lundstrom et al., 2012; Robinson et al., 2011). This spectrum has been referred to as the broader autism phenotype (BAP), and is particularly evident in first degree relatives of autistics (Maxwell, Parish-Morris, Hsin, Bush, & Schultz, 2013; Pisula & Ziegart-Sadowska, 2015). Since ALTs are so central to what we consider to be autism, they are often used as a behavioral measure with which to compare outcome measures from research studies (such as correlational analyses with neuroanatomical or -physiological findings). To estimate ALTs, several questionnaires have been developed, such as the Autism Spectrum Quotient (AQ; (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001)).

Low cognitive ability is a consistent finding in the autism literature, with 33% having intellectual dysfunction (Zeidan et al., 2022), and the average IQ being lower than in the general population, even when accounting for the increased rate of intellectual dysfunction. However, this is a nonspecific finding, as other NDDs also have decreased average cognitive ability (Forbes, Carrick, McIntosh, & Lawrie, 2009; Frazier, Demaree, & Youngstrom, 2004). On the flip side, the common variants associated with autism are associated with increased cognitive ability and educational attainment (Clarke et al., 2016; Weiner et al., 2017). This further speaks against cognitive impairment being a core feature of autism, but rather being an indirect result of negative neurodevelopmental influences in general, and suggests the presence of a clinical ascertainment bias.

Besides the generally decreased cognitive ability, there are also impairments in specific domains. One such example is that of Theory of Mind which refers to the ability to understand others and their actions by inferring their mental states. A decreased ability for Theory of Mind is one of the most consistent biomarkers for autism (Loth et al., 2021), and is certainly a strong contributor to the experienced social difficulties. Another cognitive mechanism that has been proposed is that they have weak Central Coherence (Happe & Frith, 2006), which posits that autistics have difficulties with top-down processing of information, while simultaneously having an increased ability for bottom-up processing.

A majority of autistics have alterations in sensory perception (Ben-Sasson, Gal, Fluss, Katz-Zetler, & Cermak, 2019; Leekam, Nieto, Libby, Wing, & Gould, 2007), which may express itself as both hyper- and hypo-sensitivities to any of the sensory modalities. This became part of the diagnostic criteria in the DSM-5. Autism, and indeed autistic traits across the diagnostic divide, are associated with sensory sensitivity (Horder, Wilson, Mendez, & Murphy, 2014; Robertson & Simmons, 2013). Some have hypothesized that sensory disturbances may underlie the difficulties in social communication (Marco, Hinkley, Hill, & Nagarajan, 2011; Thye, Bednarz, Herringshaw, Sartin, & Kana, 2018), such as an impaired orientation to, and processing of faces. For example, autistics show a reduced orientation toward the eye-region, an increased orientation toward the mouth-region (Ma, Gu, & Zhao, 2021; Tang et al., 2015), and decreased recognition accuracy for faces (Griffin, Bauer, & Scherf, 2021; Tang et al., 2015). The decreased orientation toward faces may be due to lower social motivation (Marrus et al., 2022) and preference for social stimuli (Moriuchi, Klin, & Jones, 2017), or from discomfort during direct eye contact (Guillon et al., 2016; Hadjikhani et al., 2017; Stuart, Whitehouse, Palermo, Bothe, & Badcock, 2022; Trevisan, Roberts, Lin, & Birmingham, 2017).

### 1.1.11 CLASSIFICATION

Classification refers to the identification of a process or condition. In the case of autism, the MDE is currently the most accurate approach to classification. However, that accuracy is contingent on a relatively high cost and low efficiency. The major promises of biological classification include improved cost and efficiency. They may also become more accurate in the near future; in particular for females and individuals with high cognitive ability, which are difficult to identify and diagnose using just the behavioral phenotype due to cognitive compensation.

The original classification of autism involved the observation of a shared cluster of behavioral phenotypes in different individuals. As science has progressed, we have learned more about the underlying biological and psychosocial processes that contribute to those phenotypes. Although it originally created awareness of the existence of the condition, there is no intrinsic reason to believe that the behavioral phenotype is the best and most powerful method for identifying autism. Similar to how the sweetness of urine has been replaced by serum glucose measurement in the identification and follow-up of diabetes mellitus, one may expect that biological methods for classification will improve in years to come, and perhaps surpass the subjective evaluations in terms of identification and prognostic ability for autism in individuals.

The importance of further development of autism classification lies in the fact that early and correct diagnosis are crucial for timely intervention and optimization of outcome. Delays in receiving a diagnosis and intervention, as is often the case, lead to inferior mental health outcomes (Rogers et al., 2012; Volkmar, 2014). This section will describe how clinical evaluations are used as the reference standard in classification studies and outline previous efforts at classifying autism.

#### 1.1.12 THE CLINICAL EVALUATION AS THE REFERENCE STANDARD FOR CLASSIFICATION

As noted in section 1.1.2, MDEs take upward of 30 hours, costing up to 60'000 Swedish krona, and the time from referral to a diagnosis may take as long as 1.5 year. Despite this lengthy and costly process, evaluations are not 100% accurate, leading to two important considerations. First, since MDEs are less than perfect, they introduce a random error into the training of classifiers that needs to be considered; because classifiers are tested against an imperfect ground truth, a superior outcome will be associated with an accuracy below 100%. To determine the superiority of a novel classification method, it will be important for individuals evaluated with such methods to be thoroughly clinically characterized and

followed up longitudinally. Second, these values are based on pre-selected samples (clinical referrals), and one may expect unselected population-based samples to have lower, and at most equal, accuracy, since the initial screening process (detection by teachers or primary care physicians) likely has a lower than perfect accuracy as well.

No studies have investigated the diagnostic agreement between MDEs, and single-clinician evaluations are likely just shy of 90% for autism spectrum disorder as a whole, and lower for specific diagnoses under the umbrella. As you will see below, many studies have shown comparable accuracies. One must be aware of these limitations when developing novel methods for classification, since the clinical utility of such methods must be compared against that of the clinical evaluations in terms of accuracy, cost, and efficiency.

One important caveat in the classification literature is the lack of validation, which extends to a limited generalizability (Steyerberg & Harrell, 2016). Most methods are applied on single samples, without replication on other samples (external validation; such as paper II in this thesis (for now)), and some fail to perform cross-validation on their sample (internal validation; such as (Ismail, Barnes, Nitzken, Switala, & El-Baz, 2017)). The DSM is now in its fifth edition, and represents decades of discussions and research, culminating in a set of phenotypic criteria with high generalizability. The lack of biological endophenotypic generalizability is the greatest obstacle to the clinical implementation of objective biological classifiers. If biological classifiers maintain their accuracy through both internal and external validation, within the range of the reference standard, there is no reason to discriminate against the clinical implementation of such classifiers, in particular if they are faster and cheaper than clinical evaluations.

A relative strength of biological classifiers is their improved efficiency, with scanning or data collection being an order of magnitude faster, and a potential for considerably lower costs. The development of a generalizable biological classifier that has the same accuracy as the clinical evaluation, but a lower cost and faster classification, would objectively be more efficient and preferable as a clinical tool.

### 1.1.13 PREVIOUS EFFORTS AT CLASSIFICATION

Many studies have been published with the aim to identify the diagnostic status of case-control cohorts through the use of various types of data, including neuroimaging, neurophysiology, genetic testing, and behavioral measures (see reviews by (Minissi, Chicchi Giglioli, Mantovani, & Alcaniz Raya, 2022; Quaak, van de Mortel, Thomas, & van Wingen, 2021; Randall et al., 2018; Song, Topriceanu, Ilie-Ablachim, Kinali, & Bisdas, 2021; Wolfers et al., 2019)). Machine learning is commonly used because of its ability to identify patterns in data, such

as systematic structural and functional neurobiological differences between cases and controls.

A large systematic review and meta-analysis by Song et al. (2021), which included 44 studies using neuroimaging data to classify autism, showed a pooled specificity of 83%, sensitivity of 86% and an AUC of .889 across all studies. The unweighted average recall (UAR; average of sensitivity and specificity) of the included studies ranged from 54% to 100% ($\mu = 80.7 \pm 12.7\%$). However, there was a significant risk of publication bias, which likely inflates these results. When including only studies with sample sizes above 100, the same values were 79%, 83% and .871 respectively. Furthermore, they found that studies using multiple data types outperformed those that used single data types, and that classification performed using the raw structural data (voxel-based analysis) was superior to using segmented morphometric data.

Deep learning, as a subtype of machine learning, has particularly high accuracy (Quaak et al., 2021), at least when used on large, high-dimensional datasets, such as from neuroimaging and neurophysiology. This might be because of decreased reliance on a priori definition of features, since deep learning algorithms perform feature extraction themselves, which limits bias and potentially improves generalizability (Mellema, Nguyen, Treacher, & Montillo, 2022).

Despite the development of very powerful methods, and a growing understanding of the phenotypes underlying autism, its classification is not entirely straightforward. There is no single approach to classification that is universally optimal, which leads to a highly heterogeneous classification literature (Quaak et al., 2021; Wolfers et al., 2019). Studies differ with regard to sample sizes and characteristics, classification methods used, approach to training, testing, and cross-validation, as well as with the use of outcome variables for estimating classification success.

Besides methodological difficulties with classification (see Quaak et al. (2021) for examples of good and bad practices; and Scheinost et al. (2019) for guidelines), there are also some limitations associated with the use of machine learning, as such methods are associated with multiple pitfalls (Bone et al., 2016; Kassraian-Fard, Matthis, Balsters, Maathuis, & Wenderoth, 2016). They require specific expertise and careful development of analysis pipelines in order to avoid such pitfalls, and in order to develop successful classification models. Although there is an increased availability of open-source classifiers with good documentation (such as scikit-learn (https://scikit-learn.org)), these issues makes such approaches somewhat inaccessible to researchers outside of the computer science field.

### 1.1.14 EXPLANATORY MODELS

As noted by Joseph (1999), the diagnostic criteria outlined in the DSM represent a relatively valid and stable consensus regarding how to identify neuropsychiatric disorders such as autism. However, it should be remembered that they are merely *ad hoc* descriptions of behavioral phenotypes, and as such a complete explanation for various findings and clinical observations across its biological hierarchy is eluded. A theoretical model must be developed that accounts for, and predicts the effects of etiological mechanisms (genetic and environmental (Bolte, Girdler, & Marschik, 2019; Weiner et al., 2017)), neurobiological and somatic endophenotypes (structural and functional biomarkers (Frye et al., 2019); immune and autonomic dysfunction (Benevides & Lane, 2015; Hughes et al., 2018)), and neuropsychological and behavioral phenotypes (Landry & Chouinard, 2016; Matson & Shoemaker, 2009). Through that account, it should be able to explain findings across the autism and psychiatric literature, such as genotypic (Robinson et al., 2013) and phenotypic sex differences (Werling & Geschwind, 2013a, 2013b), biological and phenotypic heterogeneity (Mottron & Bzdok, 2020), relationships between cognitive ability and the clinical phenotype and prognosis (Kercood, Grskovic, Banda, & Begeske, 2014), and how cognitive strengths relate to autism (Baron-Cohen et al., 2009) and its genetic architecture (Clarke et al., 2016; Weiner et al., 2017).

The idea of biological modeling has long been used in the somatic branches of medicine, with slower adoption among the psychological branches. Not unlikely due to behavioral phenotypes being complex and multifaceted, making any model of a behavioral phenotype obligatorily reductionist and incomplete. This prompted the proposal of a biopsychosocial model (Engel, 1977), which conceptually reduced the complexity of psychiatric disorders to three factors, but with inherent complexity remaining in each of the three factors. A complete psychiatric model must be able to fully incorporate the scientific literature, both across and within individual diagnoses. Obviously, as long as we do not have a full biological and phenotypic understanding of psychiatric disorders, we will not be able to develop a fully complete model. However, it is clear that one can approach completeness through improved models that are better able to explain what is already known about each disorder.

Even if we consider one of the simplest biological mechanisms, Mendelian inheritance, it is difficult to predict the biological phenotype without prior knowledge of the underlying biological mechanisms. Consider predicting the phenotypic effect of the inheritance pattern in the color of eyes or peas, without prior knowledge about allelic transmission and the existence of dominant and recessive traits (black and white would not yield grey offspring, as was first predicted, but rather one or the other). Again, the difficulty in recognizing the

underlying mechanism may stem from the absence of a theoretical framework explaining its biological mechanism.

Although the inheritance and expression of psychiatric disorders are more complex than that of Mendelian inheritance, one can extrapolate the abstraction to illustrate that careful consideration of patterns in previous generations, although not as discrete as for Mendelian traits, can contribute to the understanding of the development of psychiatric disorders in the next generation. However, increased understanding is not only achieved by elucidating contributory heritability.

Much like the identification, development, and characterization of genetic and biological mechanisms have contributed to an improved understanding of somatic disorders, the biological model view of mental illness is one that has grown, and likely will continue to do so as we uncover more about the neuroscience of human behavior and its interaction with the psychosocial environment. Although we are far from completely understanding the brain, we already have a wealth of information, allowing global mechanisms to be identified.

The development of a coherent and biologically sound model for a psychiatric disorder such as autism holds multiple promises. From such a model, one should be able to make well-founded predictions with regard to the potential presence of a psychiatric disorder in an individual, and its development, severity, and prognosis (such as stratification of newborns at risk). Another promise is the improved ability for classification. Since it is rooted in the actual contributory mechanisms of the disorder, rather than the proximate behavioral phenotype, the power of any such classifier will likely be superior to that of blindly applied big data-approaches. Furthermore, it may improve detection in groups for which the clinical interview has a notoriously low sensitivity, such as individuals with normal cognitive ability and females (Eberhard et al., 2022), by detailing how biological mechanisms interact with phenotypic compensation to influence the behavioral phenotype. Finally, the issue with heterogeneity may be a core feature of autism or stem from an incomplete understanding of its development; the closer the truth lies to the second scenario, the closer a complete model will come to entirely resolving that issue.

As we have learned more about the biology and patterns of underlying mechanisms that give rise to psychiatric disorders, the increased understanding has resulted in the proposal of a multitude of psychiatric models; both models for psychiatric disorders in general, as well as models for specific disorders such as autism. Some examples will be outlined below, to illustrate how they collectively contribute to the field and where they are lacking in relation to a theoretically complete model.

### 1.1.15 GENERAL MODELS FOR PSYCHIATRIC DISORDERS

General models attempt to outline shared mechanisms of pathophysiology for the emergence of psychiatric disorders. They *de facto* rely on findings in the literature that outline commonalities across the diagnostic divide. One such example is that of the *general psychopathology factor* (*p*-factor; (Caspi et al., 2014)), which is a factor-analytical statistical abstraction for a concept that broadly contributes to the development of psychiatric disorders (likened to how intelligence has been conceptualized as a *g*-factor). A pronounced *p*-factor is associated with a lower cognitive ability and a heightened risk of psychiatric disorders in both the proband and its relatives. Cautionary arguments have been made with respect to the interpretation of the factor structure and extrapolation to psychiatric disorders more broadly (van Bork, Epskamp, Rhemtulla, Borsboom, & van der Maas, 2017), but more importantly, the model cannot explain why individual disorders have specific difficulties (such as social difficulties in autism and impulsivity in ADHD). The authors themselves acknowledge that a 1-factor model does not fully explain their data, and that the inclusion of internalizing and externalizing symptoms provides information beyond that of the *p*-factor only (Caspi et al., 2014). This inclusion provides a small step toward specificity, which the model is lacking, since these symptoms are associated with groups of disorders (Carragher, Krueger, Eaton, & Slade, 2015), but is a long way from accommodating and explaining the development of a specific disorder.

Another example is the *developmental model of transgenerational transmission of psychopathology* (Hosman, van Doesum, & Van Santvoort, 2009). It outlines several different mechanisms by which psychiatric disorders develop, such as parental, psychosocial, and prenatal effects, and interactions with the environment, making it more comprehensive than the *p*-factor model. This allows it to accommodate for differences in life trajectories, and the development of specific types of dysfunctional behavioral patterns, compared with the *p*-factor that indicates a general dysfunction and risk across the lifespan. The authors also acknowledge genetic effects within the parental contributory mechanism, and although they present it as a general liability for psychiatric disorders, the inclusion of a genetic mechanism in the model potentially allows for some increased specificity for individual disorders compared with the *p*-factor model. However, the model lacks operationalization, which contributes to difficulties with predicting how certain dysfunctional behavioral patterns would map onto individual psychiatric disorders, reiterating the previously mentioned issue with specificity.

A third example is that of the *uniaxial model* (Craddock & Owen, 2010) which presents a framework with mechanisms across the biological hierarchy, from genetic mechanisms, through environmental interactions, to behavioral phenotypes causing a range of psychiatric disorders (on a gradient from

neurodevelopmental to affective pathology). Given the wide range of findings from across the biological hierarchy, and the inclusion of interaction effects with the environment, this model offers an important contribution to the field of psychiatric modeling. However, the model is mainly theoretical, with a low degree of operationalization. For example, the model predicts that the presence of rare genetic variants contributes to neurodevelopmental pathology, indicating a possible mechanism that connects genetic variations with the presentation of clinical syndromes (specifically, the neurodevelopmental-affective gradient) across the biological hierarchy. Unfortunately, the interactions between biological systems, neural modules, and environmental influences are merely theoretically outlined. As such, it has difficulty specifying how various alterations contribute to specific disorders, and explaining differences in patterns of clinical presentation (such as which individuals have low IQ and how that affects the phenotype).

Final examples are those of the *variable insult model* (Goyal & Miyan, 2014) and the *neurodevelopmental exposome* (De Felice, Ricceri, Venerosi, Chiarotti, & Calamandrei, 2015) which outline how endogenous and exogenous risk factors (such as genetic differences, immune abnormalities, autonomic dysfunction, and environmental toxicants) contribute to the risk of developing autism and NDDs. However, the insults outlined in the papers are not by any means specific for autism (Goyal & Miyan, 2014) or NDDs (De Felice et al., 2015), as similar findings have been found in other conditions, including affective disorders (A. S. Brown, 2015; Marangoni, Hernandez, & Faedda, 2016). Although the main focus of the papers is to outline the contribution of environmental risk factors to the development of somatic and neurological impairments that contribute to autism and NDDs, and relate that to the apparent heterogeneity, the outlined findings apply to other disorders as well. Various endogenous and exogenous risk factors contribute to neurological and cognitive impairments that render an individual more susceptible to the development of any psychiatric disorder. Similar to previously outlined models, these models do not attempt to explain the idiosyncrasies of specific disorders, and although they more or less outline how insults contribute to risk, they are not completely operationalized, making it difficult to directly apply the models in clinical practice.

In summary, these general models illustrate commonalities between different psychiatric disorders, such as cognitive dysfunctions and exposure to risk factors. However, their main issue is that they lack specificity and predictive ability with regard to individual disorders. Although psychiatric disorders often co-occur with each other in clinical practice (Gillberg & Billstedt, 2000) and share parts of the neurobiological endophenotype, individual disorders are associated with separate endophenotypes and inheritance patterns, such as autistic parents being more likely to have children with autism rather than schizophrenia. None of the presented models can explain why there is sensory sensitivity, a sex difference, or an association with cognitive strengths in autism.

### 1.1.16 SPECIFIC MODELS FOR AUTISM

There have been proposals for models that attempt to explain the features that are specific for autism. One comprehensive such model is the *intense world theory* (H. Markram et al., 2007; K. Markram & Markram, 2010). The central tenet of the model is that of a neurobiological dysregulation characterized by hyper-reactivity to sensory stimuli, hyper-connectivity and -plasticity, and hyper-fear and -memory, that collectively give rise to the autism symptomatology. The model integrates findings from across the biological hierarchy, and connects the neurobiological differences to behavioral alterations, while explaining how cognitive strengths can develop. One draw-back of the model is its inability to connect how risk factors directly contribute to hyper-functioning across biological mechanisms, since some insults would be equally, or arguably more, likely to induce hypo-functioning of a given physiological system. Although one could argue that it may induce compensatory hyper-activity, this conclusion is harder to integrate empirically, and in either case, it certainly contributes to the heterogeneity and fails to explain and predict it. Additionally, no mechanism is proposed to explain the sex differences in prevalence and phenotypic expression, nor does it integrate findings about the genetic architecture or how it relates to other disorders.

Another autism model, which was developed to address the sex difference, is the *extreme male brain theory* (Baron-Cohen, 2002). Even though there have been some difficulties with replication of studies illustrating the connection between prenatal testosterone and behavioral phenotype, possibly due to methodological constraints (Whitehouse, 2016), the deconstruction of cognitive mechanisms into a male-typical systemizing and female-typical empathizing offers an operationalized mechanism by which sex differences arise. This can potentially explain both the difference in observed phenotypes and the male-biased sex ratio. However, the theory does not integrate other findings from the literature such as the genetic architecture (other than the obligate difference in the sex chromosomes), or the role of risk factors and autonomic/immune dysfunction in developing autism or other NDDs.

A similar model, which also focuses on the cognitive differences, is that of the *weak central coherence theory* (Frith, 1989; Happe & Frith, 2006). Central coherence refers to the propensity and ability to identify global patterns in sensory information and to understand context, which is something that autistics have difficulty with. In other words, they have issues with integration of information due to an overemphasis on local features at the expense of global patterns. This is one of the postulated reasons for a decreased understanding of social communication, since such communication requires subtle signals to be interpreted in unison. The theory describes a known difference in cognitive pattern, but fails to extend the explanation down the biological hierarchy, and

does not explanation the sex difference, heterogeneity, or the role of genetic and environmental risk factors.

As a final example, the *growth dysregulation hypothesis* (Courchesne, 2002) has been presented to illustrate the neurobiological alterations that have been identified in the autism literature. It presents the autistic brain as characterized by dysregulated growth of the brain in early childhood, with generally increased growth in most areas, and normal or decreased growth in some. Although there is some heterogeneity in the neuroanatomical literature, and dysregulated growth does not occur in all autistic individuals, the model focuses on explaining the lower levels of the biological hierarchy, including the mechanisms of neuropeptides, synaptic function and brain structure. Although it may incorporate the shared effects of risk factors across NDDs (since they have been associated with dysregulated brain growth), it fails to integrate and predict cognitive and behavioral aspects.

In summary, most of the autism-specific models mainly focus on the top of the biological hierarchy (the behavioral and cognitive phenotype, which is obligately more specific for the phenomenon of autism), and are usually only able to integrate and explain narrow domains of the autism literature, while failing to integrate across the biological hierarchy. Furthermore, no such autism-specific model attempts to integrate the concepts within a broader psychiatric framework. The overlap between autism and other disorders, such as commonalities in cognitive dysfunction (Johnson, 2012) and risk factors (Moreno-De-Luca et al., 2013), may be either proximate and uncoupled with regard to biological mechanisms (consist of two different mechanisms; a case of phenotypic convergence), or ultimate and causative for the same phenotype (caused by the same mechanism; such as neurodevelopmental disruption). In other words, the cognitive dysfunction may be a core feature of each disorder, arising separately due to different influences, or be a single shared feature that arises due to a common set of risk factors. Occam's razor and the scientific literature mandate a higher plausibility for the latter scenario. In the absence of definitive empirical proof for separate mechanisms, the significant overlap between disorders requires an explanation, and implies that a theory for autism, at least for the time being, must be incorporated within a general psychiatric model in order to be complete.

### 1.1.17 REQUIREMENTS AND PROMISES OF A UNIFYING MODEL

As presented in the previous chapters, it is difficult to conceptualize a model for autism that is both sensitive enough to accommodate it within a global psychiatric framework, and specific enough to explain the idiosyncrasies of autism itself. On the one hand, there are global features that are shared between the various clinical disorders. On the other hand, there are behavioral features that are specific for

each disorder. A complete model must accommodate both of these aspects. One that is able to do that will be more complete than most, if not all, existing models.

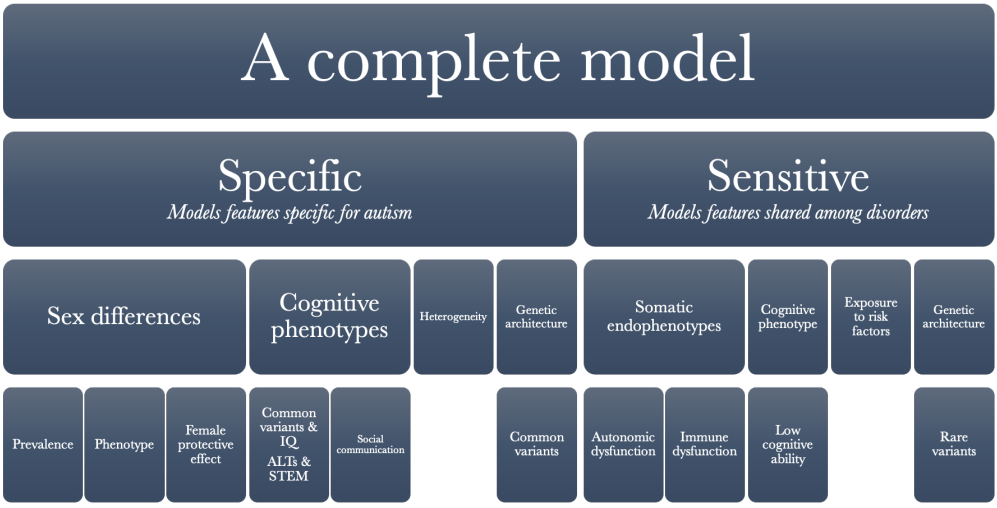


*Figure 1. Schematic outlining a theoretically complete model, which is both sensitive and specific. For a model of autism to be complete, it needs to present mechanisms that can explain what is already known, and has been shown in the literature. This includes both features that are specific for autism, and those that are shared among other disorders. The more such features a model can explain, the more it can be considered "complete". This figure illustrates a complete model using a non-exhaustive list of examples of findings in the autism and neurodevelopmental disorder literature. ALT = Autistic-Like Trait, IQ = Intelligence Quotient, STEM = Science, Technology, Engineering, Mathematics.*

Figure 1 shows an example of a model that illustrates features of autism that must be accommodated for it to be both specific and sensitive (i.e. incorporate both specific and shared features). A *sensitive* model must explain why commonalities in risk factors and neurobiological/somatic endophenotypes exist in clinical populations. These shared features likely constitute an unspecific risk and are found in clinical populations due to an ascertainment bias. Examples include an increased rate of rare genetic variants and decreased cognitive ability. A *specific* model must explain why one disorder develops and not another, and incorporate specific cognitive and psychological phenotypes. In the case of autism, it would need to explain why there are genotypic and phenotypic sex differences, why autism (in particular the subclinical phenotype) and its common genetic variants are associated with cognitive strengths, and outline mechanisms by which biological and phenotypic heterogeneity arise. Finally, for a model to be clinically useful, it also needs to be *operationalizable*.

## 1.2 METHODS FOR NEUROBIOLOGICAL CHARACTERIZATION

There are several methods for investigating and characterizing the brain, including both structural and functional ones. Similar to how the size of a muscle determines its strength, the structure of the brain will impact how it functions, and vice versa through neuroplasticity. Although the structure and function of the brain are often considered in isolation for practical purposes, for a complete understanding, one must understand both aspects.

There are many methods in practical use, each with its own set of strengths and limitations. Of the structural methods, structural MRI provides great anatomical detail, while diffusion tensor imaging allows for the mapping of white matter tracts, showing how different parts of the brain are connected. Some studies also employ post-mortem histological analysis, but this is limited to academic inquiry. Regarding the functional methods, they rely on measuring different physiological processes in the brain, such as functional MRI estimating differences in blood flow, and electrophysiological methods such as MEG and EEG measuring the electrical and magnetic fields that are generated from neural activity.

For the purposes of this thesis, which includes papers presenting data recorded with MEG and structural MRI, those two methods will be outlined more closely.

### 1.2.1 MAGNETOENCEPHALOGRAPHY

MEG is a method that allows for passive, continuous, non-invasive recording of brain activity in real-time with millisecond temporal resolution. It passively records the magnetic fields emanating from the brain, without producing a signal of its own, which differentiates it from active neuroimaging methods such as MRI, which exerts a magnetic field across the brain. MEG measures the magnetic fields outside the skull and does not require physical contact between the sensors and the subject under study. This differentiates MEG from electroencephalography and electrocorticography, which involve physical contact between an electrode grid on the scalp, and the surface of the brain, respectively. The temporal resolution exceeds that of all known neural activity, allowing for recording of brain activity at any scale. By contrast, functional MRI tracks changes in blood oxygenation in the brain, whose dynamics are limited in temporal resolution to the order of seconds. As evident, there are several significant strengths of MEG. The main limitation is that the magnetic fields are extremely weak (the earth's magnetic field is around eight orders of magnitude stronger than those generated by brain activity), and diminish with increasing distance, making

it significantly more challenging to use MEG to identify activity in deep, centrally located structures than with, for example, functional MRI.

The source of the MEG-signal is the magnetic field produced by neural activity, specifically by postsynaptic currents in dendritic projections. Such currents are the source of magnetic fields that are generated perpendicular to their direction of current travel. When thousands of neurons are simultaneously activated, a strong enough field is generated so as to be measurable outside the skull; the simultaneous activation of roughly 10'000 neurons is necessary to produce a measurable MEG signal.

In order to detect such weak signals, extremely sensitive magnetic detectors termed SQUIDs (Superconducting Quantum Interference Device) are utilized. Due to the relative weakness of the signal, environmental magnetic noise easily overwhelms it, which is why the recording must be performed within a magnetically shielded room (MSR). The MEG machine and participant are protected from environmental magnetic noise by several layers of protective metal (referred to as "passive shielding"), and the noise is additionally controlled through the use of active noise cancellation (through detection of the external magnetic field and generation of a current that produces a magnetic field that cancels it, known as "active shielding"). Furthermore, muscular contractions and heart beats also create magnetic noise, and artifacts from such sources must be removed as part of the processing (either through statistical methods, such as principal and independent component analysis (Jonmohamadi, Poudel, Innes, & Jones, 2014), or using physical assumptions about the origins of known sources, such as signal space separation (Taulu, Kajola, & Simola, 2004)).

For the SQUIDs to be superconducting, they must be kept at close to absolute zero temperature, and enclosed in a cryogenic storage dewar with liquid helium. The SQUIDs are densely packed in a helmet-shaped array that surrounds the head in order to maximize spatial sampling (and thus spatial resolution) while minimizing the distance between each sensor and the brain.

Potential analyses of MEG-data include event-related fields (ERF), source localization, connectivity, and spectral analyses (for examples of analyses using Minimum Norm Estimate (MNE), see https://mne.tools).

### 1.2.2 MAGNETIC RESONANCE IMAGING

Structural MRI is a non-invasive method that uses magnetic fields to generate signals allowing the structure of the brain to be visualized with high spatial resolution. As opposed to some other structural imaging methods, such as computed tomography, MRI does not utilize ionizing radiation. However, since

it employs strong magnetic fields, it is contraindicated for individuals that have metallic implants. Because the scanning times can be long, and the magnet produces loud noises, it can be uncomfortable, in particular for individuals with claustrophobia.

MRI works by aligning the magnetization direction of hydrogen nuclei in the body through the application of a strong external magnetic field (a primary magnetic field). In other words, the MRI magnet produces a slight net magnetization across the body. By applying pulses of radio waves, one is able to manipulate the spin direction of the hydrogen nuclei, which give off a signal as they move back to their original, slightly non-random, spin directions. Spatial encoding is enabled by the application of a magnetic field gradient (a secondary field), which varies in strength across the body and alters the resonance frequency of the spins, making it possible for the signal location across the primary magnetic field to be identified. This allows for the origins of the signals to be heralded to their three-dimensional positions in space. Since hydrogen atoms are particularly numerous in fat and water, these are the main tissues that produce the signal.

The structural images that are produced are commonly used for identification of pathology in a hospital setting, and they can also be used for morphometric analyses. Previously, manual morphometry was used in the research setting, where the outline of a given structure was marked for each section through the structure. This allowed for volumetric analyses to be conducted on brain structures *in vivo*, but was a tedious process and very time consuming. The advent of automated software for brain segmentation has ushered in an era of scalable morphometry, vastly increasing the number of structures and participants that can be analyzed. One such software is FreeSurfer (Fischl, 2012) which segments the brain into gross morphological tissues (such as gray and white matter, and cerebrospinal fluid), and delineates specific regions of interest, such as cortical and subcortical structures, according to specified anatomical atlases.

Scanning participants with both MEG and MRI allows for the data to be co-registered in space, and the brain activation to be heralded to specific areas. One approach to this is by extracting the cortical outline using FreeSurfer, and constraining the MEG-signal to the cortex (which is the principle for MNE (Gramfort et al., 2014) used in paper III).

# 2 AIMS OF THESIS

There were four aims of the thesis. ***First***, to develop and operationalize a theoretical model for NDDs in general, and autism in particular, that can incorporate existing findings in the literature and provide empirical predictions and testable postulates. ***Second***, to develop and test a simple statistical method for multivariable classification, not requiring specific expertise, and compare it against machine learning methods. ***Third***, to investigate neurophysiological signatures of face processing, and identify potential differences between autistics and neurotypical controls. ***Fourth***, to investigate how gamma oscillations in the visual cortex relate to visual motion sensitivity, and investigate potential group differences between autistics, known to have sensory alterations, and neurotypical controls. Each of the aims has been addressed in a separate paper (see Table 2 below).

*Table 2. Aims of thesis and papers addressing each aim*

| **Aims** **Papers** | **I** | **II** | **III** | **IV** |
|---|---|---|---|---|
| Develop a theoretical model for neurodevelopmental disorders | ✓ | | | |
| Develop and test a multivariable classification method | | ✓ | | |
| Investigate neurophysiological group differences in face processing | | | ✓ | |
| Investigate visual gamma oscillations and their relationship with visual motion sensitivity | | | | ✓ |

# 3 MATERIALS AND METHODS

Paper I is based on a transdisciplinary focused literature review of autism and related fields, such as neuropsychiatry, neurodevelopment, immunology, and autonomic physiology.

Papers II-IV are based on a cross-sectional study (hereafter referred to as *the study*) using an autism-control sample. The participants, the collection, processing and analysis of data, the statistical analyses used, and ethical considerations are outlined below.

# 3.1 PARTICIPANTS

## 3.1.1 RECRUITMENT

The participants were recruited from longitudinal cohorts at the Gillberg Neuropsychiatry Centre (GNC, Gothenburg, Sweden), through the GNC website (www.gu.se/gnc), and using advertisement in the local newspaper (GöteborgsPosten).

The control group was self-selected through the website and newspaper advertisement. The patient group was recruited from two ongoing longitudinal studies at the GNC (for more detailed descriptions of the cohorts, please refer to (Davidsson et al., 2017) and (Helles, Gillberg, Gillberg, & Billstedt, 2015) respectively). The individuals had been diagnosed with autism using both the DSM-4 (American Psychiatric Association, 1994) and the International Classification of Diseases-10 (World Health Organization, 1992) on at least two or three separate occasions separated by five years or more, indicating highly stable diagnoses. One patient was recruited through the website, and his diagnosis was verified through a review of his medical records.

## 3.1.2 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for both groups were male sex and an age of at least 18 years, and an autism diagnosis for the patient group.

Exclusion criteria for both groups were any neuropsychiatric diagnosis (other than autism in the patient group), an IQ below 80, epilepsy, metallic implants, claustrophobia, and non-correctable low visual acuity.

## 3.1.3 SAMPLE CHARACTERISTICS

We used a case-control sample consisting of age- and IQ-matched adult males. The participants were matched pair-wise across groups so that the age did not differ by more than 5 years, and full-scale IQ by 10 points, and the final sample was tested for significant group differences. The patients that had completed IQ-tests as part of the longitudinal studies were not re-tested.

One autistic and all the controls were IQ-tested by a psychologist following recruitment. IQ scores were missing for two autistics and one control, but they had completed university degrees and/or were living independently, which are associated with floor-effects with regard to IQ. Furthermore, one autistic was included with a full-scale IQ of 78. However, he could not complete the final subtest due to excessive sleepiness (on which he scored below 60, four standard

deviations below average) indicating a high likelihood of having a full-scale IQ above 80 had he been able to complete the test.

The age at MEG-scanning was 30.6 ± 7.1 years for the autism group and 27.8 ± 6.5 years for the control group ($p$ = .17). IQ scores were 109.8 ± 15.1 and 114.3 ± 11.4 for the autism and control group respectively ($p$ = .28).

The AQ score was missing for one autistic. The autism and control groups scored 23.8 ± 8.8 and 11.2 ± 6.3 respectively. Although there is a highly significant difference ($p$ = 0.000003, $d$ = 1.67), both groups scored lower than compared with reference values in the population (35.2 and 16.9 respectively; see (Ruzich et al., 2015)). Considering subclinical ALTs as part of the same spectrum as the core autism symptomatology (Lundstrom et al., 2012; Plomin, Haworth, & Davis, 2009), this would imply that the groups are less "autistic", but more importantly also less differentiated than expected, which likely contributes to decreased power and an underestimation of group differences using the present sample.

The Adolescent/Adult Sensory Profile (AASP; (C. E. Brown & Dunn, 2002)) score was missing for two autistics. The autism and control groups scored 33.7 ± 8.0 and 26.2 ± 7.0 for *low registration*, 40.6 ± 6.2 and 48.4 ± 6.0 for *sensation seeking*, 35.7 ± 9.6 and 30.9 ± 7.4 for *sensory sensitivity*, and 37.5 ± 7.4 and 31.0 ± 7.4 for *sensation avoiding*. Compared with the normative values provided in the questionnaire (for a neurotypical adult population), our sample scored within the average range for all subscales, except for a slightly lower sensation seeking in the autism group. Our participants scored in the same ranges as the autism-control sample in Kuno-Fujita et al. ((2020); except their control group scored lower than the normative values on sensation seeking).

### 3.1.4 SAMPLE SIZES

We recruited 47 individuals: 25 autistics and 22 controls. One autistic was identified during the MEG recording as having epileptic activity, and was excluded from the sample and referred to a physician. This left a total sample size of 46 (24 autistics and 22 controls) that were scanned using MEG and MRI. One control had normal visual acuity, and was included in the study, but was later identified as being nearly blind on one eye, and was therefore excluded from the visual MEG experiments (papers III and IV).

Since papers II-IV were based on different types of data and experiments, they also differed with regard to their specific inclusion and exclusion criteria. Paper II used only structural MRI data, and due to delays with obtaining data from one control, the sample size was 24 autistics and 21 controls. Papers III and IV are based on MEG data. Due to issues with co-registration of MEG and MRI data,

excessive noise levels, and partial blindness for two autistics and two controls, paper III included 22 autistics and 20 controls. Analysis and publication of paper IV was completed during the project and before the entire sample had been recruited and undergone scanning with MRI and MEG, which is why that sample included 20 autistics and 19 controls.

It is worth noting that all the analyses for each paper were performed after the sample for each substudy had been determined and completed scanning, implying that there is no effect of sampling bias on the outcomes of the substudies.

# 3.2 ASSESSMENT INSTRUMENTS

## 3.2.1 INTELLIGENCE TESTING

The Weschler Adult Intelligence Scale-IV (WAIS-IV; (Wechsler, 2008)) and the Weschler Intelligence Scale for Children-IV (WISC-IV; (Wechsler, 2003)) were used to test cognitive ability. WISC-IV is used for children aged between 6 years and 16 years and 11 months, and WAIS-IV for individuals over the age of 16 years. Both WAIS and WISC had been used in the longitudinal studies, and WAIS-IV was used for testing in the present study if there was no previous test result.

These tests are administered by a psychologist, and estimate not only the full-scale IQ, but also the ability within the four subdomains: verbal function, perceptual function, working memory, and speed. Results are normalized for each age with 100 as the average, using a standard deviation of 15. The subtests for verbal function measure verbal ability, expressiveness, and the ability to understand concrete and abstract concepts. Those for perceptual function reflect the ability to integrate visual stimuli and to find logical patterns, the ability to mentally rotate and join figures into a larger shape, as well as fine motor skills. Working memory tests reflect the executive functions, and test the ability to retain and manipulate information while maintaining attention. The subtests for speed estimate the speed of learning new information, visuo-motor skills, visual discrimination, and visual short-term memory.

## 3.2.2 AUTISM SPECTRUM QUOTIENT

The AQ (Baron-Cohen et al., 2001) was used to estimate the number of ALTs in both groups. It is a self-report questionnaire consisting of 50 questions such as "I notice patterns in things all the time" and "I find social situations easy". Responses are recorded on a four-point Likert-scale ("Definitely agree", "Slightly agree", "Slightly disagree", and "Definitely disagree") with a binary scoring (1 or 0 for either "agree" or "disagree") depending on the item's association with an ALT. The sum across items gives a total AQ-score in the range of 0–50.

The total AQ is normally distributed in the population (Ruzich et al., 2015) with autistics scoring on average 35.8 (SD = 6.5) and controls scoring 16.4 (SD = 6.3). The lack of floor-effects that are otherwise seen with many clinical instruments (which usually have a standard exponential distribution where many individuals score low or zero, and show low sensitivity for subclinical traits), indicates an ability to estimate subclinical ALTs in the general population. Even though the AQ has shown good internal consistency and test-retest reliability (Baron-Cohen et al., 2001; Hoekstra, Bartels, Cath, & Boomsma, 2008), there are some concerns

regarding its specificity due to increased scores in other neuropsychiatric disorders, such as schizophrenia (Lugnegard, Hallerback, & Gillberg, 2015).

### 3.2.3 ADOLESCENT/ADULT SENSORY PROFILE

The AASP (C. E. Brown & Dunn, 2002) is a 60-item self-report questionnaire that gauges an individual's sensitivity to sensory stimuli in a variety of sensory domains, including visual, auditory, touch, and temperature. Responses are given on a five-point Likert scale (from 1 to 5): "Almost never", "Seldom", "Occasionally", "Frequently", "Almost always". The total score is calculated (ranging from 60 to 300), as well as that of four subdomains (ranging from 15 to 75): "Low registration", "Sensation seeking", "Sensation avoidance", "Sensory sensitivity". The results for each subscale are compared against normative scales provided in the questionnaire. The normative results are based on neurotypical samples separated by age using sample sizes of $n$ = 193 for 11-17 years, $n$ = 496 for 18-64 years, $n$ = 261 for >65 years.

For paper IV, since we were interested in gauging neurophysiological responses to moving visual stimuli, we developed our own scale for visual motion sensitivity by combining the scores for the two items: "*I am bothered by unsteady or fast moving visual images in movies or TV*" and "*I become bothered when I see lots of movement around me (for example, at a busy mall, parade, carnival)*".

# 3.3 PROCEDURES

Broadly, the participants were informed about the project and gave their informed consent to participate before they were screened for inclusion and exclusion criteria, and were given self-report questionnaires to fill out. They then underwent brain MRI scanning at the Sahlgrenska University Hospital in Gothenburg and MEG scanning at the Swedish National Facility for Magnetoencephalography (NatMEG; www.natmeg.se) at the Karolinska Institute in Stockholm.

## 3.3.1 INITIAL MEETING

All participants, either following an eligibility check from within the longitudinal studies or after expressing interest to participate in the study, were contacted by post or phone to set up an initial meeting for information, recruitment, and testing.

During the initial meeting, participants were informed about the study, including ethical aspects, and were allowed to ask questions before signing the consent form. The participants received 1'000 SEK after tax, and were reimbursed for lost salary and travel costs during each phase of the study, even if they opted out (including for the initial information meeting, before signing the consent form, if they declined to participate altogether). The participants were informed about the possibility to discontinue their participation in the project at any point. After signing the informed consent, the participants were screened for inclusion and exclusion criteria by a medical doctor using a checklist, and tested using WAIS-IV by a licensed psychologist if no previous test result was available.

## 3.3.2 DATA ACQUISITION

### 3.3.3 QUESTIONNAIRES AND INTELLIGENCE TESTING

Both groups filled out a set of questionnaires, including the AQ and AASP. See section *3.2. Assessment instruments* for descriptions of the instruments that were used. The participants were given the option to fill out the questionnaires after the information meeting, or in the privacy of their homes and then mail them back to the GNC. The responses were recorded into an anonymized master file containing each participant's code and their responses for each item and questionnaire.

### 3.3.4 STRUCTURAL MRI

T1 weighted sequences of the brain were acquired using the FreeSurfer recommended sequences (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999) depending on the manufacturer of the MRI machine that was used

(Siemens: MPRAGE; GE: FSPGR-BRAVO; Philips: TFE-TENSE). For specific acquisition parameters, see Paper II. Seven individuals had performed brain MRI on a Siemens 3T scanner during a previous study at Lausanne University Hospital. The rest were scanned at Sahlgrenska University Hospital (Östra Sjukhuset and Sahlgrenska Sjukhuset). Each MRI was reviewed by a neuroradiologist for the presence of pathological findings, and the data was saved on DVDs labeled with each participant's code.

## 3.3.5 MAGNETOENCEPHALOGRAPHY

### 3.3.6 PREPARATIONS

For the MEG scanning, the participants traveled to NatMEG. They were instructed to wash their hair on the day of scanning, and not use hair products or wear jewelry. Upon arrival at the lab, they were informed about the procedure, given a tour of the lab, and encouraged to ask questions regarding the preparations and scanning.

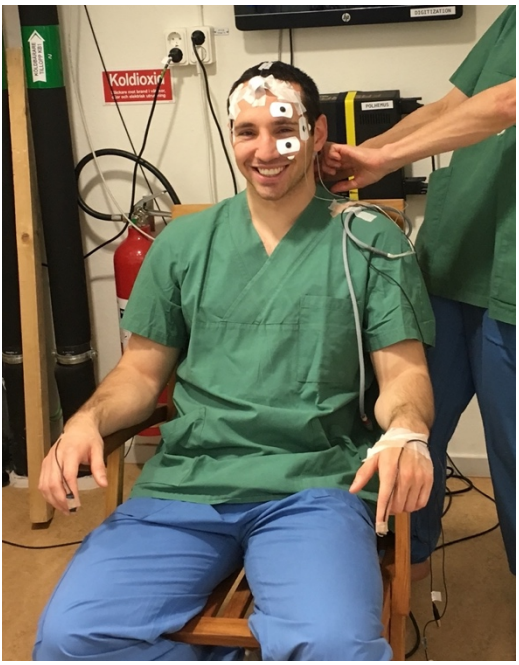


*Figure 2. Participant preparation involves placement of electrodes and head position indicator-coils, and digitization of coil positions, head shape, and fiducial points.*

As part of the preparation, the participants changed to MEG-compatible non-magnetic clothes. They were asked which hand was dominant. If they used glasses or lenses, MEG-compatible glasses with the same diopter were used throughout the scanning. Electrodes were placed laterally to the eyes (horizontal electrooculography-channel), above and below the left eye (vertical electrooculography-channel) to control for blinks, on the neck (ground), on the palm of the non-dominant hand (galvanic skin response), and below the left clavicle (electrocardiography-channel). They were then seated on a wooden chair and Head Position Indicator-coils (HPI) were placed on their heads (on the mastoid processes and the top of the forehead bilaterally; see Figure 2). The positions of the HPI-coils and their head shapes were digitized in three-dimensional space using a Fastrak system (Polhemus Inc., Colchester, VT). The positions of the HPI-coils were digitized

before and after the head shape, and the difference between the positions was tested using an in-house script to make sure their positions were accurate and stable. If the difference was greater than 3-4 mm, the digitization process was repeated.

Before the participants entered the MSR, an empty room recording for 5 min at a sampling frequency of 5000 Hz was performed to estimate system and environmental noise levels. After being seated in the 306-channel MEG-system (Elekta Neuromag TRIUX; see Figure 3), the electrodes were connected to the MEG-machine, an accelerometer was attached to the index finger of the dominant hand, and a respirometry belt was placed around the thorax. Pillows were used to make sure that the participants were seated comfortably and snugly, with the head in contact with the helmet.

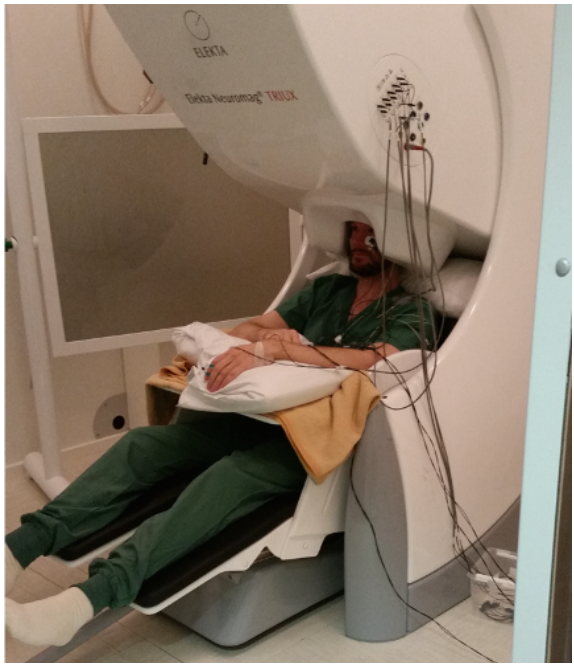


*Figure 3. Positioning in the MEG scanner*

A back-lit presentation screen was placed 1 m in front of the participants, with a MEG-compatible eye-tracking system (Eye-link 1000) mounted on the bottom of the screen. Before starting the experimental paradigms, the eye-tracking system was calibrated, and the signals from the MEG-channels were visually inspected for artifacts and noise. When such were detected, the corresponding MEG-sensor was heated and re-cooled to superconducting temperatures. If the noise level was not deemed adequate after several attempts, the channel, and any affected nearby channels, were noted for exclusion during the pre-processing stage of data analysis. The MSR used dimmable lights, and the lighting was always set to the same intensity.

### 3.3.7 EXPERIMENTAL PARADIGMS

Three experimental paradigms were used: resting state, faces and pareidolic objects, and moving circular gratings. The resting state paradigm lasted 5 min at

the beginning and end, and was recorded with a sampling frequency of 5000 Hz. The other paradigms were recorded at 1000 Hz, and took 16-50 min each.

For the resting state paradigm, the participants were instructed to look at a fixation cross in the middle of the screen and not think about anything in particular.

The paradigm using the face stimuli consisted of two sessions. The first session (OBJECTS) used real faces (F), pareidolic face-like objects (FLO), non-face objects (O), and inverted neutral faces as stimuli. The second session (EMOTIONS) used real faces with various facial expressions (happy, angry, scared, and neutral), as well as inverted neutral faces. Before each stimulus was presented, a fixation cross was presented at the center of the screen. The participants were instructed to press a button whenever they saw an inverted face (control stimuli) in order to maintain vigilance throughout the recording.

The paradigm using the moving circular gratings presented black and white gratings moving concentrically with three different speeds (slow: 1.2°/s, medium: 3.6°/s, fast: 6.0°/s). Each presentation was preceded with a fixation cross, and participants were instructed to press the button whenever the movement stopped. Brief cartoon animations were presented at random intervals between stimuli to maintain vigilance.

### 3.3.8 ACQUISITION PROCEDURE

The paradigms were used in the following order: resting state, OBJECTS, half of the stimulus presentations with the gratings, EMOTIONS, the other half of the gratings, resting state (see Figure 4). The total time for information, preparation, and scanning was 2,5 hours on average. Following each paradigm, the participants were asked to rate how sleepy they felt on a 10-point Likert scale. Pauses were made if participants requested, or if they were visibly tired. Participants were then offered something to eat or drink, and were allowed to stand up. Before the start of each paradigm, and after pauses, the head position inside the MEG helmet was checked visually, as well as using an in-house script to make sure the head was positioned close to the helmet. The MEG traces were again inspected visually for noisy channels, and heated if necessary. Head position was continuously monitored during scanning. Throughout the experiment, there was a two-way

auditory connection between the MSR and the lab, and a one-way visual connection using a camera mounted in the MSR.

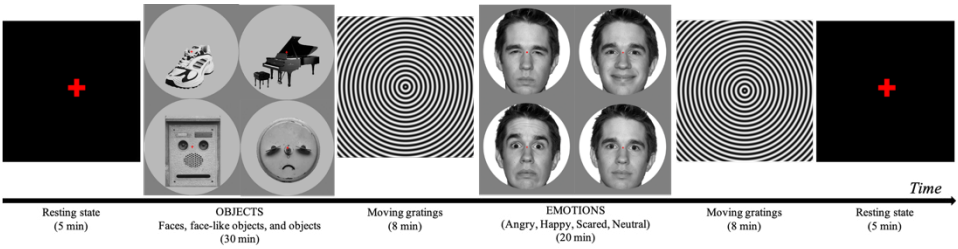


*Figure 4. Experimental paradigms used during MEG-recording (adapted from illustration by Bushra Riaz)*

## 3.3.9 DATA PROCESSING AND ANALYSIS

The general steps of processing and analysis will be outlined first, followed by the specific processing and analysis performed in each paper.

### 3.3.10 STRUCTURAL MRI

The automated segmentation software FreeSurfer v6.0 (Dale et al., 1999; Fischl et al., 1999) was used for brain segmentation. FreeSurfer provides morphological data about the volumes ($mm^3$), areas ($mm^2$), and thicknesses (mm) of cortical regions of interest (ROI), as well as the volumes of subcortical, and cerebellar gray and white matter structures. The Desikan-Killiany atlas was used for segmentation (see Figure 5 for the segmentation of a representative individual). In order to allow for comparisons of source estimated MEG activation patterns across participants, each individual's brain structure (geometric distribution of gyri and sulci) was morphed onto an average brain template.

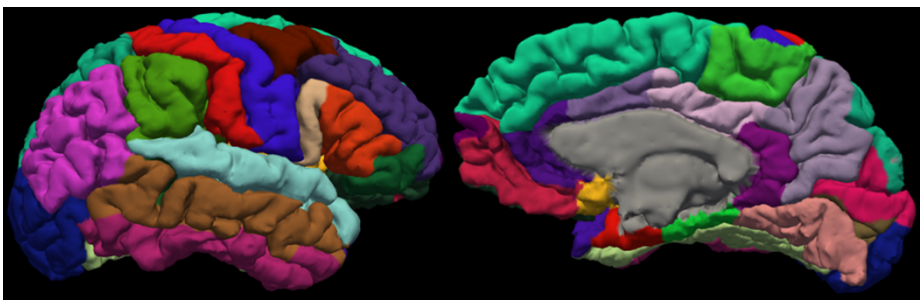

*Figure 5. Example of a cortical parcellation using FreeSurfer for a representative individual*

The ROI measurements for the left and right hemispheres are reported individually, as well as global measures such as total intracranial volume, total gray and white matter volumes, subcortical gray matter volume, and left and right

hemisphere volumes. Furthermore, segmentation enables demarcation of the outlines for the white and gray matter, as well as the skull, which is used to create the Boundary Element Model, which is later used for source reconstruction of the MEG signal.

MNE-Python is used to produces a source space model based on the individual's brain with a distribution of current dipoles across the cortex. Current dipoles represent magnetic generators; in this case, clusters of current in postsynaptic dendritic projections. The source space and boundary element model can be fused with the MEG data (using the HPI-coil position within the helmet) to calculate the forward solution, which represents the expected activation patterns at the MEG sensors when specific dipoles are activated.

### 3.3.11 MULTIVARIABLE CLASSIFIER

In paper II we present a multivariable classifier which we developed and tested using the morphometric data from the brain MRI segmentations. Briefly, the method consists of four steps (see Figure 6 for equation).

$$TI_n = \sum_{p=1}^{q} \left( \left( \frac{x_n^p - \mu_\mu^p}{SD_\mu^p} * \frac{\mu_A^p - \mu_B^p}{\left|\mu_A^p - \mu_B^p\right|} \right) * \left( \left| \frac{\mu_A^p - \mu_B^p}{SD_\mu^p} \right|^2 * \frac{\mu_A^p - \mu_B^p}{\left|\mu_A^p - \mu_B^p\right|} \right) \right)$$

*Figure 6. Equation used for multivariable classification. The total index TI for each individual n is calculated with the following equation. The left bracket consists of interindividual comparison (measurement x for parameter p in individual n is subtracted from the average of the group averages for p) and z-normalization (by dividing with the average standard deviation of the groups for p). This is multiplied with the sign function, which is +1 for p's where group A has a larger average than B, and -1 where B is larger. The right bracket consists of weighting, which involves calculating the absolute effect size for p and squaring it (although other functions, or larger exponents may be used for greater discrimination among p's) and multiplying with the sign function to maintain directionality. The functions within the outer brackets yield a value for each measurement, in terms of its relation to the pattern of group averages, and the values for all p's are summed to give the TI for each individual.*

*First*, each ROI measurement from the brain segmentation is z-normalized, so as to have comparable units and magnitudes, and decrease overestimation of importance of naturally larger structures. *Second*, each ROI is weighted depending on their ability to separate cases and controls. This is done by calculating the effect size (Cohen's *d*) for each ROI across groups, which is multiplied with each individual's measurement for that ROI. *Third*, an inter-individual comparison is made for each ROI by subtracting an individual's measurement from that of the average of the group averages, yielding a positive or negative score depending on direction and closeness to each group's average. For example, if the right hippocampus is significantly larger in the cases than the controls, and an

individual has a right hippocampus that is larger than the midpoint between the group averages, then it receives a large positive index score. ROIs with smaller differences between cases and controls are weighted less (smaller *d*) and thus yield smaller indices, allowing the classifier to discriminate between ROIs depending on their importance for classification. Also, the weighting and inter-individual comparison are multiplied by a sign-function, which constrains the patterns for cases and controls to positive and negative values respectively. *Finally*, the indices for each ROI are summed, to produce a Total Index-value (TI) for each individual. This outcome variable is a continuous measure of the gross morphological pattern of each individual's brain. It indicates how much, and how often the measures of an individual align with that of the average case or control.

Since the group averages and effect sizes were calculated using data from the current sample, we used Leave-One-Out Cross-Validation (LOOCV) to prevent statistical circularity. In LOOCV, one individual is excluded from the training set, and the effect sizes and averages for each parameter are calculated on the remaining *n-1* participants. The method is then applied on the individual parameter measurements for the excluded participant and a TI is calculated for the excluded participant. This is repeated for each participant in the study.

Four machine learning algorithms (decision tree classifier, logistic regression, support vector machine, neural network) were compared with our classifier. Since the performance of these algorithms is positively associated with the size of the dataset, we only performed classification using all datasets combined (i.e., all the segmentation measurements). The same approach was used, with LOOCV, split randomization, and no random seed, with calculation of the UAR following 5000 iterations.

### 3.3.12 MAGNETOENCEPHALOGRAPHY

The general pipeline for MEG analysis and source estimation is presented in Figure 7, and involves the preprocessing and analysis of functional MEG data, and fusion with the structural MRI data for estimation of source activations. The recording was performed with active shielding, and Elekta proprietary software MaxFilter was used to remove the shielding signal and that of the residual magnetic noise (using the noise covariance matrix). Temporal Signal Space Separation (Taulu, Kajola, et al., 2004; Taulu, Simola, & Kajola, 2004) was used to further reduce environmental magnetic noise (from outside the helmet), and to correct for head movement during the recording. The raw data was band-pass filtered, and noisy channels and data sections were annotated, after which it underwent dimensionality reduction and artifact removal (heart beats and eye blinks) using Independent Component Analysis (ICA; (Jonmohamadi et al., 2014)). The ICA-solution was then exported to be applied on the raw data before analysis.

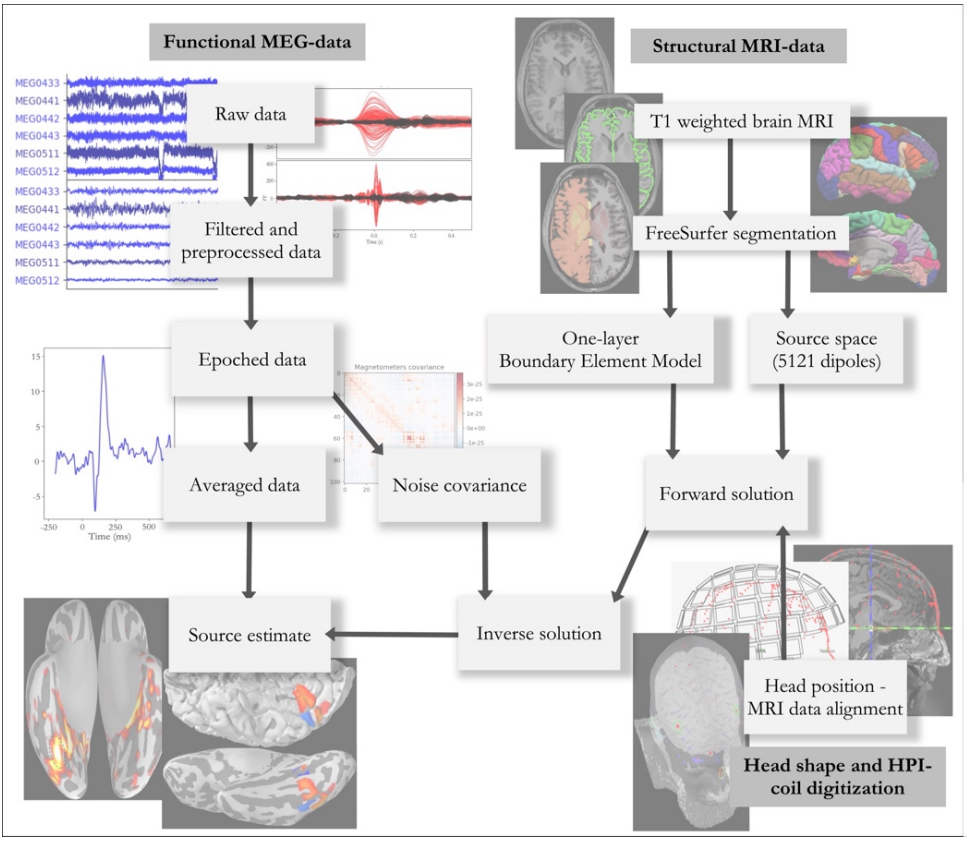


*Figure 7. Pipeline for MEG data pre-processing and analysis. HPI = Head Position Indicator, MEG = Magnetoencephalography, MRI = Magnetic Resonance Imaging*

The preprocessed data was epoched, which involves cutting the data around the stimulus presentation (for example .5 s before and 1 s after). The epoched MEG data was visually inspected, and noisy epochs were removed. Epoching allows for averaging of the event related activation (MEG time-series amplitude in response to a stimulus) for each stimulus type. A noise covariance matrix was estimated using the MEG data, which together with the forward solution was used to find an inverse solution. Applying the inverse solution to the MEG data allows for visualization of the estimated real-time source activations (current dipole activations as a function of time) at different locations in the brain.

**MEG analysis in Paper III**

Briefly, the analysis in Paper III consisted of the following steps. The paradigm with emotional face stimuli (EMOTIONS) was used to identify the area of maximal response to faces in the right fusiform gyrus (in the anatomical source space), and the paradigm with F, FLO and O (OBJECTS) was used for further analysis. The ICA-solution, from the pre-processing step, was applied on the raw OBJECTS-data, which was then band-pass filtered between 1–40 Hz. The data were epoched around stimulus presentation (200 ms before to 800 ms after) and epochs were baseline-corrected using the 200 ms pre-stimulus interval. The source space activation within the previously defined area in the FFA was calculated and averaged across presentations for each individual to get the ERF for each stimulus type. The entire time-series for the individual ERFs were saved for use in cluster-based permutation testing. We also identified the peaks of the M170 (the maximal ERF amplitude in the time window 150-170 ms post-stimulus), and the M130 components (the last peak with opposite polarity before the M170), and exported their absolute latencies and average peak amplitudes (10 ms before and after the peak), as well as the average amplitude of the late component (within the time window 400-550 ms) for use in a mixed model ANOVA.

**MEG analysis in paper IV**

The FieldTrip M/EEG toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) and the Dynamic Imaging of Coherent Sources inverse solution algorithm (Gross et al., 2001) were used to localize the anatomical sources of the gamma activity. The frequency window used for gamma activity was estimated from the MEG sensor level peak gamma frequency, and group differences were tested for significance using cluster-based permutation testing. Linearly Constrained Minimum Variance Beamformer was used to find the peak frequencies and power ratios for each individual within 25 voxels of the maximally active voxel during stimulus presentation.

The gamma power was estimated for each individual and speed of stimulus movement (slow, medium, fast), and used to calculate the coefficient of regression. Since the power is suppressed with increasing speeds, the regression coefficient is negative. This coefficient was termed the GSS and was extracted for further analyses.

### 3.3.13 STATISTICAL ANALYSES

Unless otherwise specified, an $\alpha$-value of $p = .05$ was used to indicate statistical significance[2]. Two-tailed independent samples Student's T-tests were used for group comparisons (unless otherwise stated), and ANOVA was used when testing more than two independent variables (mixed model in paper III and one-way in paper IV). If assumptions for parametric testing were not met, non-parametric tests, such as Kruskall-Wallis were used. For correlational analyses, we used Pearson and Spearman correlations for when parametric assumptions were, and were not met, respectively. Bonferroni or Holm-Bonferroni (HB) corrections were applied within independent sets of observations. SPSS (versions 24, 26, 28 in papers IV, II, III respectively) was used for statistical analysis of discrete data points (such as ANOVA). In-house python scripts were developed for cluster-based permutation tests of continuous and multidimensional data (such as time-series). For training and testing in classification, leave-one-out cross-validation was used. For the continuous outcomes (TI) in paper II, the receiver operating characteristic was calculated, including the area under its curve.

Cluster-based permutation testing, which was used in paper III, is a non-parametric method for statistical testing of large datasets (such as time-series) that is automatically corrected for multiple comparisons (such as measurements at different time-points). Permutation testing is used to compare two conditions, and makes use of randomization of group labels (if comparing autism and control, the column with diagnostic labels is shuffled). One then calculates the T-statistic for each time-point, and identifies the largest area under the curve for T-values above those corresponding to the predetermined $\alpha$-value. By iterating the process of randomization and calculation of the largest area under the curve, one gets a distribution of expected cluster sizes under the assumption that the two samples are drawn from a single population with no difference. If the size of the cluster in the actual, non-randomized data, is larger than that of the 95-th percentile (if using a 5% $\alpha$-threshold), one concludes that the compared groups are significantly different. For more specific descriptions of statistical analyses, please refer to each individual paper.

[2] Hereafter, when using the term *significant*, it is referring to statistical significance

## 3.4 ETHICAL CONSIDERATIONS

The study was ethically approved by the Regional Ethical Review Board in Gothenburg, Sweden (DNR: 552-14). All procedures followed the principles in the Helsinki declaration of 1975, as revised in 2008, including considering and minimizing potential harm, upholding confidentiality of the participants, gathering informed consent, allowing participants to withdraw without specifying reason, etc.

No data was recorded prior to signing of the consent form, including the checking of inclusion and exclusion criteria (other than the information already gained regarding diagnostic status from the previous longitudinal studies). Pseudonymization was used, in which all the data was coded, and each individual received an individual code. The code key was kept separate from the data, to which only the involved researchers had access. The questionnaires were recorded without personal information, using only the personal codes. The MEG and MRI data were pseudonymized and the files were named according to the personal code.

Participation in the study implied a considerable time investment by the participants. For this they were financially reimbursed, both through loss of salary for each step of the study, any incurred expenses on testing days (such as food and travel), and through a payment of 1000 SEK after tax.

Regarding performing research on autistics, there were a couple of specific considerations. The patients had all (except one, who contacted us himself, as did the control group) been part of previous longitudinal studies, and had expressed interest and given consent to be considered for participation in future studies. Since behavioral rigidity and difficulty with novel situations are typical of the autistic phenotype, care was taken to minimize these issues for both groups, but the autistics in particular. The primary contact at the onset of recruitment was done by mail, and the participants were asked to contact us by mail or phone, and they were alerted that they would be contacted by phone to set up the initial meeting. Extensive effort was made to make the participants comfortable ahead of, and during, the scanning procedures. For the trip to Stockholm, all participants were offered a personal chaperone. They were offered to visit the MEG and MRI labs prior to scanning, in order to facilitate accommodation, and they were given textual and visual step-by-step descriptions regarding the scanning procedures and facilities. In order to make the participants relaxed about being closed inside the MSR, they were informed about a two-way auditory connection with the lab, and that the researchers could see them through a video stream, and they were instructed on how to open the MSR from the inside.

There are specific considerations also with regard to the data collection methods. Both MRI and MEG are non-invasive and non-ionizing scanning methods. MEG is entirely passive, and records brain activity without documented negative side effects. The stimuli presented during the MEG scanning use standard experimental setups that have been used in previous studies without any documented negative effects. Due to long scanning times, the participants were given breaks, and reminded to request breaks if they felt tired. MRI images are generated by applying a magnetic field and measuring signals resulting from changes in the magnetization of the body, and the method is not associated with any detrimental effects. However, individuals with metallic implants need to be excluded, as they are incompatible with MRI imaging. Furthermore, claustrophobia may be a complicating factor for both methods, and all participants were asked about this prior to recruitment and shown the scanning procedure in case they were unsure about being claustrophobic.

Since some medical conditions can be identified using brain MRI and MEG, the MRI scans were reviewed by a neuroradiologist, and the MEG-data was inspected for epileptic activity. In the case of any worrisome features, the participant was referred to the hospital for follow up. This was also the case for any suspected conditions that were reported or identified during the screening procedure.

# 4 RESULTS

## 4.1 PAPER I – A THEORETICAL FRAMEWORK

The paper outlines and operationalizes three factors that interact to cause a clinical phenotype which we associate with a given NDD: 1) the Disorder Personality Type (DPT), 2) Cognitive Capacity (CC), and 3) the Neuropathological Burden (NB).

Briefly, the DPT is operationalized as a non-pathological personality dimension (such as the BAP, a schizotypal personality, etc.). These dimensions arise mainly because of polygenic effects, which are specific for either individual disorders (such as autism or ADHD) or biologically related groups of disorders (such as schizophrenia and bipolar disorder) (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Opel et al., 2020). The polygenic effects are postulated to give rise to disorder-specific intermediate endophenotypes (Mattheisen et al., 2022; Opel et al., 2020), which are associated with different behavioral phenotypes (such as ALTs or schizotypal traits). If a pronounced DPT is coupled with a relatively low CC (operationalized as intelligence and executive functions), the individual is unable to compensate for, and cope with the traits stemming from that phenotype. This leads to a maladaptive behavior that may be identified as fulfilling diagnostic criteria for a clinical diagnosis. The development of the CC, pre- and postnatally, is impeded by various exogenous (infections, toxins, etc.) and endogenous insults (stress, rare genetic variants, etc.), which together make up the NB. Due to their intricate relationship, NB and CC can be jointly considered as an NB/CC-complex. NB/CC-complex dysfunction is shared among the disorders and increases the risk of any NDD though clinical ascertainment; the greater the dysfunction, the higher the risk of fulfilling criteria for any one, and multiple diagnoses.

## 4.2 PAPER II – AUTISM CLASSIFIED BY MRI

The morphometric results showed multiple significant group differences (I only present those that were significant following correction for multiple observations). The autism group had larger subcortical volumes for the right thalamus, bilateral hippocampi, and left nucleus pallidus, as well as thicker cortices for the right parahippocampal, bilateral entorhinal, right fusiform, left anterior cingulate, and right inferior and superior temporal cortex. The control group had a thicker pericalcarine cortex bilaterally. Cortical areas significantly differed between groups only for the bilateral inferior temporal cortices and the left banks of the superior temporal sulcus (larger in autism). White matter volumes showed no significant group differences after correction for multiple observations.

The cross-validated continuous outcome variable from the classifier, the TI, was calculated for each dataset, and used for calculation of the UAR (which ranged from 73.2–78.9%) and the AUC (which ranged from 0.714–0.792). The best accuracy was achieved using subcortical volumes, which had the highest UAR and AUC.

The Pearson correlation coefficient between each individual's TI estimated from different datasets and their AQ-scores, showed significant correlations when using all data, as well as for the individual datasets, except cortical thicknesses. The strongest association was a moderate statistically significant positive correlation for the subcortical volumes.

The binary outcomes from the algorithms were compared against the true diagnostic status, which yielded the following accuracies following LOOCV: decision tree classifier 67.5%, logistic regression 58.1%, support vector machine 56.8%, neural network 53.6%. Our classification method produces a continuous outcome, allowing for optimization of the diagnostic threshold. The raw accuracy of our classifier, when using 0 as the cut-off, was 66.1%, which increased to 73.2% when optimizing the threshold.

## 4.3 PAPER III – FACE PROCESSING AND FUSIFORM ACTIVATION

For the discrete components, we found across-group differences for M130 and M170 amplitudes (lower for O), M170 latency (earlier for F), and the late component (higher for F). There were within-group differences in the M170 amplitude (lower for O in both groups), and the late component (lower for O than F in the control group). The only between-group difference was a lower M170 amplitude in the autism group (across stimulus types), which was not significant after correction.

For the continuous event related fields, we found across-group differences between all stimuli, and a within-group difference between F and O in the control group. There were no between-group differences, nor within-group differences in the autism group.

We also performed permutation testing on source-space activations across the cortex and compared stimulus types across all participants. There was a spatial cluster in the area corresponding to the right FFA when comparing FLO and O (in the time window 150-170 ms) and F and O (130-150 ms).

## 4.4 PAPER IV – GAMMA OSCILLATIONS AND SENSORY SENSITIVITY

The autistics had a marginally higher general sensory sensitivity than the control group (average total AASP scores of 37.7 and 31.2 respectively), but there were no significant group differences in the AASP-derived measures of visual sensitivity.

Gamma response power showed a strong inverse relationship with velocity, but there was no group difference or interaction effect. There was a strong positive relationship between peak gamma frequency and velocity, but no group or interaction effect.

There were moderate significant correlations between GSS (a measure of the change in gamma oscillation in response to varying speed of moving visual stimuli) and self-reported sensory sensitivity, both across and within groups. For visual motion sensitivity, there was a moderate correlation across groups, strong correlation for the autistic group, and no significant correlation for the control group. In other words, weaker suppression of the gamma response predicted increased sensory sensitivity in general and visual motion sensitivity specifically (except for the control group).

There were no significant group differences with regard to gamma oscillation total power, average location of the maximally induced voxel (in the left calcarine sulcus), nor between any of the measures of the AASP and peak gamma frequency or gamma response power ratios.

# 5 DISCUSSION

Although an overt phenotypic pattern, such as described in the DSM, represents a generalizable consensus, it will be associated with covert endophenotypes and contributing mechanisms. Reverse-engineering the underlying mechanisms is necessary, but less straight forward than mere phenotypic description.

To do so, one must develop theoretical models that not only encompass the multitude of endophenotypic and phenotypic signatures of autism, but also correctly predict their associations and effects. For example, the finding that CNVs contribute to risk can be ascribed to two potential models: 1) a direct model, where they lead to the development of autism, and 2) an indirect model, where they increase the risk of a diagnosis through a negative effect on cognitive ability. Both models accurately describe the association between CNVs and autism, but only one will align with the true causative mechanism and be generalizable across samples and methodologies. In this example, the indirect model would likely fail to find an association in a sample with normal cognitive ability, while the direct model should find associations of similar effect sizes irrespective of the cognitive ability of the sample. The latter is less plausible since autistics with normal IQ have CNV-rates similar to that of the general population (Huguet et al., 2018). This implies that CNVs are not an inextricable part of the autism phenomenon, which is supported by their presence also in other NDDs.

The example illustrates how one may identify covert causative mechanisms, which are then assembled to create a model. Not only can improved models allow us to better understand autism; biological classification can be improved by relying on such models to guide feature selection, and through the development of the statistical methods used for classification. This illustrates why a multimodal approach is necessary.

The study used for papers II-IV, and the aims that have been addressed in each of the papers, will be discussed in separate subchapters below.

## 5.1 THE STUDY USED FOR PAPER II-IV

For papers II-IV, a case-control cohort was used in a cross-sectional design. Similar to most other single-site studies, the total sample size of 46 is on the low end, and constitutes a general limitation. This is especially true with regard to classification studies, since one is able to create more accurate predictions when training the classifier with larger samples. A larger sample size allows for higher accuracy and greater generalizability. Another issue of small sample sizes is that it limits the possibility of performing subgroup analyses, which is of particular importance for heterogeneous conditions such as autism, and would have contributed positively to analyses performed in papers II-IV. On the other hand, when considering clinically relevant phenomena, which have larger effect sizes, it is also possible for a study to be overpowered (Friston, 2012). Significant group differences in a limited sample size, particularly after correction for multiple observations, require strong effect sizes. Studies that use hundreds to thousands of participants have higher power, and can identify minuscule differences. However, such findings are less useful in clinical practice and for personalized medicine, which speaks for the relevance of the findings in this thesis.

A major strength is that the patient group has been well phenotyped with highly stable diagnoses, having fulfilled the diagnostic criteria for autism on all, but at least two separate occasions (except one individual who was not recruited from the longitudinal cohorts). That the diagnostic accuracy of the clinical interview is not 100% (see section 1.1.2), and that some individuals may eventually improve to the point of not requiring a diagnosis (Anderson, Liang, & Lord, 2014; Helt et al., 2008), usually constitute limitations of studies with a cross-sectional design. The confidence in the clinical phenotypes of our patient group is therefore a considerable strength in comparison with many other studies. Furthermore, since most individuals with autism receive their diagnosis in childhood (Solmi et al., 2022), the recruitment of only adult participants strongly limits the number of false negatives. Although it would have been preferrable, we did not perform full neuropsychiatric assessments on our control participants, but this is less of an issue in an adult sample, since one may expect that the majority of individuals that will receive an autism diagnosis will have done so. For this reason, classification studies using younger samples should place greater emphasis on limiting false negatives since they are more likely to constitute errors in classification, as opposed to false positives.

On a similar note, a potential limitation is that the control group was self-selected. This might induce a bias, such that individuals who self-identify as autistic, or that have autistic relatives (who also have more ALTs than the general population), are more likely to show interest in taking part in a study about autism. This may

be the reason for the slightly lower relative group difference in mean AQ in our sample compared to population norms (separated by 1.3 and 2.3 mean standard deviations respectively; (Ruzich et al., 2015)). Since relatives of individuals with autism, and undiagnosed individuals with pronounced ALTs (Billeci et al., 2016; Frye et al., 2019) have more similar endophenotypes to autistics, it would be preferable to exclude control participants that have an autistic relative or an AQ above a certain threshold. Although the lower group differentiation in terms of an autistic phenotype may represent a methodological limitation, it constitutes a strength in relation to the findings in the papers. The sampling of slightly less differentiated groups decreases power and necessitates higher effect sizes for identifying significant differences, which indicates their robustness.

Since only adult males with normal IQ were included, the results do not generalize to large parts of the clinical population and replication studies using such samples are necessary. Our plan was to replicate the study using a female sample, but due to issues with obtaining the full funding amount, that plan has been put on hold. The finding of an association between GSS and sensory sensitivity (Paper IV) has been replicated in a female sample (Manyukhina et al., 2021)). The narrow sampling can be rationalized through the pathogenetic triad; the inclusion of a normal-IQ sample limits heterogeneity, and the exclusion of children limits noise in the data associated with developmental aspects. Although the papers in this thesis cannot conclude which findings belong to which feature in the pathogenetic triad,[3] one can expect endophenotypes and phenotypes stemming from the NB/CC-complex to be more pronounced if replicated in a female sample (because the female protective effect predicts more exaggerated group differences in female samples for features that are associated with risk factors). The same is likely true for a sample with lower average IQ.

Because the results in papers II-IV are based on the same sample, there is an aggregate risk of a type I error. It is not standard procedure to correct for multiple observations across studies, in particular since one might not be certain of the number of future observations and publications using the sample. However, when considering multiple findings in a thesis ad hoc, one must be aware of the increased risk of type I errors, at least for observations based on covarying datasets (such as neuroanatomical and neurophysiological data). An alternative is to perform Bonferroni correction of the $\alpha$-level post hoc for the findings in the included papers. In this case, that would imply dividing the employed $\alpha$-levels by three (HB-thresholds in paper III, Bonferroni-corrected thresholds in paper II

[3]However, as an example, cortical thickness provides a solid classification accuracy in paper II, but is not correlated with the AQ. This may indicate that it is more likely to represent an expression of the NB/CC-complex, than of the personality domain.

and $\alpha$-level in paper IV). Doing this would change none of the results in the papers, except for the disappearance of a main effect of stimulus for M170 latency across groups, and differences between F-FLO and FLO-O across groups (within ANOVA and permutation tests respectively in paper III).

## 5.2 PAPER I

The requirements for a complete and unifying model for NDDs was outlined in section 1.1.17. Briefly, such a model must be able to integrate both autism-specific findings from across its biological hierarchy (provide the model with specificity), but also allow the phenomenon of autism (or any individual diagnosis) to be conceptualized within a more general model that incorporates findings from other disorders as well (provide sensitivity). This paper outlines an etiological model for NDDs that fulfills such criteria and it has several major contributions.

Contrary to existing general psychiatric models – such as the psychopathology-factor (Caspi et al., 2014), the variable insult model (Goyal & Miyan, 2014), and the dominant de novo model (Sebat et al., 2007) – this framework is able to incorporate findings that are specific for each disorder. Although general models successfully delineate commonalities among the disorders, they fail to provide explanations for why autism-related genes are associated with high rather than low IQ, why females with autism are less frequent but more affected, and most crucially, why someone gets a particular disorder such as autism and not schizophrenia. For example, by framing the BAP as separate from the NB/CC-complex, it is the only general framework that can accommodate the association between the polygenic burden for autism and an increased cognitive ability (Clarke et al., 2016; Weiner et al., 2017). Existing models that can predict an increased ability either fail to incorporate it physiologically (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006), or do not present a connection between the common variants and the phenotype they postulate as causing the increased ability (Baron-Cohen, 2002, 2009; K. Markram & Markram, 2010). The main reason for the specificity of the framework is that each DPT is vertically integrated across the biological hierarchy, and each is postulated to be associated with different common variants, giving rise to different disorder-specific intermediate endophenotypes (Mattheisen et al., 2022; Opel et al., 2020), themselves resulting in different behavioral phenotypes. Within the DPT-feature of the model there is little overlap between disorders, which is illustrated by co-occurring disorders showing additive patterns in endophenotypic studies. Furthermore, sex differences in social cognitive ability (CC) and biological vulnerability (NB) may explain why there is a difference in prevalence and phenotype.

On the other hand, it also integrates research findings across disorders, which is something that models specifically developed for autism fail to do. Although the mind-blindness theory describes a decreased ability for theory of mind (Baron-Cohen, 1995), the growth dysregulation hypothesis predicts an increase in brain size in early childhood (Courchesne, 2002), and the weak central coherence theory describes a cognitive bias for scale (Frith, 1989), they do not extend to other levels

in the biological hierarchy, and they fail to incorporate the phenotypes of other disorders. In other words, they do not explain why and how risk factors overlap among the NDDs, such as alterations in sensory processing, specific cognitive phenotypes, or rare genetic variants (Brownstein et al., 2022; Fernandes, Cajao, Lopes, Jeronimo, & Barahona-Correa, 2018; Gudmundsson et al., 2019; Kern, Geier, Sykes, Geier, & Deth, 2015; Warrier et al., 2022). The pathogenetic triad postulates that risk factors share a common etiological pathway through neurodevelopmental inhibition, which decreases cognitive ability and adaptive ability, leading to a clinical ascertainment. Which diagnosis an individual fulfills criteria for depends on their genetic susceptibility from common variants and their DPT profile.

These two contributions jointly solve a major limitation in the field of psychiatric modeling by creating a universal model that allows for findings to be conceptualized within a singular framework. Thus, one can identify how features relate, or do not relate, to each other across disorders. One way in which this can improve academic and clinical inquiry is that it may allow for the resolution of contributing mechanisms (NB/CC-complex dysfunction and DPT as being separate).

Unlike other comprehensive models, which are usually theoretical and descriptive, (such as the developmental model of transgenerational transmission of psychopathology (Hosman et al., 2009) or the uniaxial model (Craddock & Owen, 2010), the pathogenetic triad is operationalized and presents approaches for quantification. This makes it practically useful, as clinicians and researchers can apply it directly on their patients, guiding both clinical decision-making and the planning of research studies.

For clinicians, a pronounced BAP in the parents or over-transmission of common variants (Weiner et al., 2017) in conjunction with multiple deleterious CNVs in offspring, particularly in the presence of pregnancy-related complications, should alert them to the potential need for counselling, and an increased vigilance for development of autistic symptoms. Identifying the co-occurrence of these features can narrow down the number of families that are more closely followed for development of autistic symptoms, outside of just focusing on siblings of diagnosed probands. Furthermore, identifying NB/CC-complex dysfunction, because of its prognostic importance, may be more important than labeling the phenotype of a particular disorder. Such dysfunction is often a greater predictor of outcome than any particular diagnosis, and is associated with a higher number of co-occurring disorders. "Lumping" by NB/CC-dysfunction, and "splitting" by the individual profile of DPTs may be an etiologically sound solution to the standing question of lumping vs. splitting of diagnoses in neuropsychiatry

(Cuthbert & Insel, 2013; Marquand, Wolfers, Mennes, Buitelaar, & Beckmann, 2016) The pathogenetic triad represents an etiological approach, which is similar to the clinical ESSENCE-approach outlined by Gillberg (2010).

For researchers, the idea that the autistic phenotype and NB/CC-complex constitute separate etiological mechanisms may prompt the use of a three-group case-control setup (as presented below) to allow the contributing effects of each mechanism to be ascertained. It also provides a causative model within which researchers can frame their findings. For example, rather than autism with high and low IQ representing different conditions with separate inheritance (due to common and rare variants respectively; (Gamsiz et al., 2015)), common variants contribute to both (Gaugler et al., 2014; Weiner et al., 2017), but the presence of highly penetrant rare variants yields a phenotype that includes impaired cognition (as it does for neurotypical individuals; (Huguet et al., 2018; Rolland et al., 2022; Warrier et al., 2022)). Another example is the conclusion that different clinical conditions are related (such as autism, ADHD and schizophrenia) simply because they share cognitive deficits or deleterious genetic variants (Gudmundsson et al., 2019; Kern et al., 2015). The alternative explanation, that they are separate conditions which are clinically ascertained with regard to NB/CC-complex dysfunction, is more in line with findings that the conditions have separate endophenotypic (Opel et al., 2020) and genotypic signatures (Mattheisen et al., 2022; Stanfield et al., 2008; Weiner et al., 2017).

Ultimately, complete model may help the field overcome the issue with heterogeneity (Molloy & Gallagher, 2021; Mottron & Bzdok, 2020). It imparts a problem for clinical evaluations and scientific studies, and limits the discriminant validity of biological classifiers by decreasing the power of individual biomarkers (Loth et al., 2021). The heterogeneity has been shown to increase in conjunction with cognitive dysfunction (Ambrosino et al., 2022; Mattheisen et al., 2022), and most of the biological heterogeneity is postulated to stem from NB/CC-complex dysfunction. This refers specifically to the effect of risk factors; it goes without saying that even if one were to remove all the biological heterogeneity due to risk factors, the biological and phenotypic homogeneity will never exceed that of the neurotypical population due to a natural variation in personality, such as extroversion-introversion, and psychosocial experiences. Dissection of the concept of autism into three contributing features, and implementation of insult characterization is proposed as an approach to limiting heterogeneity through stratification according to biologically relevant contributors from the NB/CC-complex (Molloy & Gallagher, 2021; Unwin, Maybery, Wray, & Whitehouse, 2013).

The framework implies there is a clinical ascertainment bias of two distinct features and their co-occurrence; one pertaining to the specific personality domains and one pertaining to the effects of neurodevelopment. Assuming the clinical syndrome of autism arises due to the co-occurrence between an autistic personality and the joint effect of cognitive compensation and environmental risk factors, then that is important to consider when planning future studies. If one does not correct for both ALTs and IQ, or use a three-group case-control design (autism – autistic personality – prototypically neurotypical) one invariably confounds two variables, which diminishes power and the conclusions that can be drawn from the study, as well as contributing to the heterogeneity. The moderating effect of intelligence is well known, and IQ is commonly controlled for. But, although many studies also record ALTs, they often use instruments that are associated with floor-effects and are therefore not sensitive to the distribution of traits outside the clinical intensities; this is only marginally better than just considering the diagnostic status.

If the presented framework is closer to the true etiopathogenesis than current models, and represents an improvement of our understanding of autism, it should also yield improved classification results. The operationalization presented in Paper I was tested using data from the study. By recording the AQ, a heart rate variability (HRV) measure for vagal function, and the working memory subscale of WAIS, we were able to achieve a high diagnostic resolution (an area under the receiver operating characteristic of 97%, 95%CI [.91-1.00]; (Sarovic et al., 2019)). However, since this is based on a convenience sample, the specificity and generalizability of the result need to be investigated through the inclusion of other NDDs, females, and individuals with lower cognitive ability.

However, the framework is not without its limitations. It is based on a focused literature review of selected publications, which may be biased, requiring each aspect of the framework to be supported by a systematic review. Also, since the framework was developed with autism in mind, it needs to be revisited in light of the full scientific literature for schizophrenia, ADHD, etc. Finally, it is a framework with a strong developmental aspect (in particular the concept of the neuropathological burden). Although the interaction between cognitive compensation and the behavioral phenotype may extend to conditions that are considered to be less developmentally and biologically determined, such as personality disorders or affective disorders, the framework may be less accurate for such disorders and likely requires revision and extension in order to accommodate such disorders; the inclusion of a psychosocial factor as a moderating variable may allow the framework to be extended to psychiatric disorders other than the NDDs. Finally, HRV as a putative marker for the NB

has not been studied with regard to its longitudinal effects on brain and cognitive development, and such studies are warranted.

## 5.3 PAPER II

The main contribution of the paper is in presenting a novel method for multivariable classification which is simpler to use than machine learning, requires no expertise, and is transparent. The complexity and black-box nature of machine learning algorithms make such methods less available to clinicians and researchers, and present obstacles to their wider implementation in classification (Bone et al., 2016; Kassraian-Fard et al., 2016). Despite this, they are frequently used in the classification of autism, with UARs ranging between 51–100%, with an average of 80.6±12.7% (for meta-analysis, see Song et al. (2021); also (Ingalhalikar, Parker, Bloy, Roberts, & Verma, 2011; Libero, DeRamus, Lahti, Deshpande, & Kana, 2015; Sabuncu, Konukoglu, & Alzheimer's Disease Neuroimaging, 2015; Uddin et al., 2011; Zhou, Yu, & Duong, 2014)).

In the current sample, our classifier achieved a mean UAR of 75.7% (average UAR for the tested datasets), and a maximal classification UAR of 78.9% using subcortical volumes (sensitivity 76.2%, specificity 83.3%), which is on par with the summary ROC average of published classification studies (see figure 5 in the meta-analysis by Song et al. (2021)). In other words, the maximal accuracy in our paper is comparable to the average accuracy in the literature. However, one of the main contributors to the issue with replication of research findings is that small single-site studies have more variable outcomes than larger multi-site studies. For the same reason, subsets of data have larger variability than entire datasets, and there is a chance that individual subsets have high performance (such as the subcortical volumes in our dataset). Looking at the overall mean accuracy in our study, it is around the 40th percentile, and likely slightly higher since some of the published studies did not perform cross validation, and there was evidence of a publication bias in the literature.

We also found that our classifier outperformed the machine learning algorithms, with a maximal accuracy of 73.2% compared with <67.5%, when tested on all the morphometric measurements. This was an unexpected finding, and may be due to the limited size of the dataset, since such algorithms generally thrive in much larger datasets. If future studies replicate a superior performance using small to modest (or perhaps large) datasets, one may recommend the wider implementation of our classification method for such datasets.

A potential development of the method is that one may substitute the weighting by using functions rather than the effect size, which can be defined using a continuous variable, such as the AQ. This would allow the method to predict a continuous, rather than a binary, outcome, and widen the areas where it is applicable.

The locations of the morphometric group differences are mainly clustered around the same regions as those presented in previous studies, such as subcortical, limbic, and temporal areas. These areas have been shown to be important for key cognitive domains such as social cognition and repetitive behaviors, and the interpretation of sensory information and its integration with internal states (for neuroanatomical review see Ecker (2017)).

The finding that structurally estimated TIs correlate with AQ across groups supports previous findings and indicates that the neuroanatomical pattern is associated with ALTs across the diagnostic divide (not only with subclinical ALTs (Arunachalam Chandran et al., 2021; Blanken et al., 2015), but also with autistic symptom severity (Ecker et al., 2010)). Since classification studies using functional data seem to have a slight advantage over structural data (Song et al., 2021), one may assume that the biological alterations underlying autism and ALTs are more functional than structural. But more importantly, it illustrates that both are necessary for a complete picture, and that multivariable classification using both types of datasets is likely optimal. This conclusion is supported by studies that used combinations of data achieving the highest classification accuracies (Libero et al., 2015; Song et al., 2021). We have preliminary results (unpublished data) showing higher accuracy, up to 87%, when the classifier is applied on connectivity-measures from MEG.

## 5.4 PAPER III

Our overall findings indicate that there are no group differences in the early components to suggest that autistics have alterations in the processing and differentiation of stimuli containing basic facial features. This implies that face detection is unimpaired, at least in our sample of individuals with normal IQ. It has previously been suggested that autistics have decreased activation in response to faces (Bailey et al., 2005; Kovarski et al., 2019; Sysoeva, Constantino, & Anokhin, 2018), but these findings may have been confounded either by a lack of stimulus fixation (Perlman, Hudac, Pegors, Minshew, & Pelphrey, 2011) or by differences in cognitive ability (O'Connor, Hamm, & Kirk, 2005, 2007). Our recruitment of a normal-IQ sample and use of a pre-stimulus fixation cross may explain the lack of group differences at the early components.

The late component was found to differentiate real faces from non-face objects across groups, illustrating that higher post-stimulus latencies are associated with greater relative sensitivity to real F, even compared with pareidolic O. This finding has been variable in the literature, with some studies showing the same pattern (Churches et al., 2009; Wardle, Taubert, Teichmann, & Baker, 2020) and others not (Hadjikhani et al., 2009). Studies that have employed familiar faces and emotional expressions have found increasing differences with higher latencies (Apicella, Sicca, Federico, Campatelli, & Muratori, 2013), possibly due to the recruitment of higher cognitive processes (such as memory) and top-down modulation. At higher latencies, there is time to receive additional neural input, such as with regard to the social information content of the stimulus (which faces contain). When comparing within group differences, we found that the control group had significantly higher amplitudes for F than O, with no differences in the autism group. The lack of group differences at the early components, and differences at the late component, may be interpreted as the autism group having intact face detection, but possibly either being less sensitive to the additional social information content in the actual F stimuli, or due to disengagement. Autistics are often sensitive to, and dislike, direct eye contact (Stuart et al., 2022), and our F stimuli showed direct gaze. It has been suggested that decreased attention for social information in early childhood may underlie the subsequent development of sensitivity to direct gaze (Moriuchi et al., 2017), implying that decreased FFA activation may develop due to lack of experience (Foss-Feig et al., 2016). Since we used an adult sample, we cannot conclude whether the late component difference is due to decreased sensitivity for social information or disengagement.

A strength of our study is the use of source space activation; rather than relying on detecting activation of temporal sensors, which have variable positions with regard to underlying brain regions (Gross, Schnitzler, Timmermann, & Ploner,

2007), we identified activation in the FFA. Although face processing has been extensively investigated, at least with regard to early components and using faces and non-face objects, a limitation is the low generalizability of the sample. Studies replicating our methodology (including FLOs, higher post-stimulus latencies, and looking at source space activation) on females, children, other NDDs, and low-IQ individuals are necessary.

## 5.5 PAPER IV

We found that the GSS was associated with sensory sensitivity, both across and within groups. The GSS was also associated with our visual motion sensitivity scale in the autism group and across groups. The finding in the control group was borderline significant, and given the similar association for sensory sensitivity there may be a difference, albeit with a smaller effect size, which may reach significance with a larger sample size. The GSS is a novel neurophysiological marker of sensory sensitivity, and the robustness of our finding is supported by a replication study that used the same methodology on another sample and found the same result (Manyukhina et al., 2021).

It has been suggested that the features underlying the GSS are determined by properties of the E/I-ratio, and in particular with that of the excitatory drive (Orekhova, Prokofyev, Nikolaeva, Schneiderman, & Stroganova, 2020; Orekhova et al., 2018). Previous studies have suggested that an alteration in the E/I-ratio is a central mechanism in the development of autism (Hussman, 2001; Rubenstein & Merzenich, 2003; Uzunova et al., 2016). Although sensory sensitivity may be more pronounced in autistics, the significant association across the diagnostic divide suggests that the sensitivity and its relationship to the GSS may be a continuous rather than a discrete phenomenon. In other words, the alteration is likely not associated with the autism diagnosis per se (a binary phenomenon due to the presence of a risk factor), but rather with an extraneous physiological mechanism. Orekhova et al. (2020) found that the steepness of the GSS correlated with IQ in children, illustrating how low-level properties of neural networks underlying the E/I-ratio may be associated with higher cognitive functions.

In some cases of E/I imbalance it is possible to manipulate the E/I-ratio pharmacologically (Canitano & Palumbi, 2021). Given the relationship between the GSS and the E/I-ratio (Orekhova, Prokofyev, et al., 2020; Orekhova et al., 2018), the GSS may be used as a therapeutic biomarker during interventions with such medications, to objectively gauge therapeutic effects. There are studies that have shown changes in behavioral (Hadjikhani et al., 2018; L. Zhang et al., 2020) and biological (Hadjikhani et al., 2018) phenotypes following administration of pharmacological agents that affect the E/I-ratio. However, none have used direct biomarkers of the E/I-ratio to indicate that such changes are associated with known underlying mechanisms, making it difficult to ascertain what is driving the behavioral and endophenotypic effects.

Although a general limitation of our study is the low generalizability, since only adult males with normal IQ were included, the association between the GSS and sensory sensitivity has since been replicated in a female sample (Manyukhina et

al., 2021). Until the finding is replicated in children and individuals with low IQ, we cannot generalize our findings to such populations.

The scores for the subscales of the AASP for the autism group were comparable to those of a previous study (Kuno-Fujita et al., 2020), with both samples scoring slightly below normative values for sensation seeking. Our control group scored within the average normative values across all subscales. This implies that the control group, and likely also the autism group, are representative, in terms of sensory sensitivity profiles.

# 6 CONCLUSIONS AND FUTURE DIRECTIONS

The main conclusions for each of the papers in this thesis are:

I. *First*, the proposal that the disorder personality type and the NB/CC-complex comprise separate constructs, and relate differently to the underlying etiology, biology, and the clinical expression. *Second*, that there is a clinical ascertainment bias for NDDs due to NB/CC-complex dysfunction, and that risk factors converge on a pathway of neurodevelopmental inhibition. *Third*, the suggestion that the heterogeneity mainly results from NB/CC-complex dysfunction, and that insult characterization can be used for stratification.

II. *First*, our novel statistical method for multivariable classification, which is simpler to use, does not require expertise, and is more transparent than machine learning algorithms, performed on par with such methods in the tested dataset. *Second*, the finding that there are systematic group differences in terms of neurobiological measurements that allow for objective biological classification to be performed, and this study adds to that literature. *Third*, the individual morphometric findings align with previous studies and indicate neuroanatomical group differences in the subcortical, limbic and temporal areas.

III. Face detection is unimpaired in autism, but there is decreased right FFA activation at higher latencies, which may imply a disengagement from faces, or decreased integration of the social information they contain.

IV. The identification of the gamma suppression slope as a biomarker for self-rated sensory sensitivity. It may be used as a therapeutic biomarker to investigate outcomes in intervention studies.

There are several avenues for continuing the research presented in this thesis. First and foremost, the validity of the pathogenetic triad needs to be corroborated by systematic reviews that focus on the main proposed mechanisms and the postulates of the model. Furthermore, longitudinal clinical and population-based studies will be instrumental in showing its ability to model autism and make correct empirical predictions, and to show that its operationalization improves clinical reasoning and classification accuracies. Although our pilot classification study showed a high classification accuracy (Sarovic et al., 2019), it needs to be

replicated in larger samples without group-matching, and externally validated before it can be clinically implemented. In particular, the proposed separation between the disorder personality type and the NB/CC-complex needs to be corroborated by future studies that sample different NDDs.

For the pathogenetic triad to be used in categorization, there is a need to develop specific instruments for estimating the disorder-associated personality types. Questionnaires such as the AQ also gauge cognitive function and overlap slightly with other behavioral phenotypes (for example, items such as "I can keep track of several different people's conversations" or "I find it hard to make new friends"), implying that it is not capturing the core autistic personality mutually exclusively from the NB/CC-complex and other DPTs. Instruments specifically aimed at measuring the core, mutually exclusive traits of each personality type need to be developed in order to better quantify the personality domain. There is also a need for studies that apply the pathogenetic triad for risk stratification, such as using polygenic and rare variant risk scores for risk prediction.

Estimating the NB/CC-complex is easier said than done. It has been argued that it is difficult to predict the risk associated with specific rare genetic variants, since their mechanisms are unknown (Thapar & Rutter, 2020). However, assuming they increase the risk of a NDD diagnosis by decreasing cognitive ability, studies should instead focus on quantifying their negative effect on cognitive ability, and that magnitude be used for genetic counseling. The pathogenetic triad predicts that stratification according to insult characteristics, such as the type of rare genetic variant, may improve homogeneity, and more studies performing such stratification are needed (similar to the one by Unwin et al. (2013)). Besides insult characterization, quantification of autonomic function is presented as a possible approach to capture the variability and effect of the NB/CC-complex, and longitudinal studies ascertaining the role of HRV in relation to the development of NDDs are warranted.

The current state-of-the-art in neurobiological classification is the use of multivariable classification, such as machine learning algorithms (Song et al., 2021). An increasing proportion of studies include multiple datasets (both structural and functional), and this development will likely continue (Turner, 2014). Currently, the major obstacle to the continued development and subsequent clinical implementation of neurobiological classifiers is the lack of external validity. This is partly for intrinsic reasons, such as biological heterogeneity (Reiter et al., 2021), and partly for extrinsic reasons, such as small sample sizes. These issues are being addressed with the development of large, multi-center repositories of neuroimaging data (such as ENIGMA and ABIDE: enigma.ini.usc.edu; fcon_1000.projects.nitrc.org/indi/abide/). However, such

datasets are inherently more heterogeneous than single-site studies (in terms of diagnostic evaluations, data collection, and/or data processing), and there are efforts to create improved and more standardized pipelines for data collection and processing (Andersen, 2018; Knudsen et al., 2020; Tummala, Thadikemalla, Kreilkamp, Dam, & Focke, 2021; Vandekar & Stephens, 2021) which will limit intrinsic biases. Ultimately, classifiers will need to be implemented and tested in clinical settings, in which case they need to be evaluated in terms of their accuracy and their benefits to clinical practice. There is a dearth of research that studies clinically implemented classifiers, by comparing them with outcomes from, and effect on efficiencies of neuropsychiatric evaluations. Furthermore, the lack of empirical estimation of the accuracy for best practice in diagnostic evaluations (MDEs) is a limitation that needs to be addressed. This may be done by comparing agreement between blinded MDEs performed by multiple teams on the same sample. As long as there is no such estimate, it is difficult to argue that an objective biological classifier may have an adequate performance and should be clinically implemented, other than as a supplement to increase efficiency.

The specific neuroanatomical and neurophysiological findings presented in this thesis need to be replicated in other, more clinically relevant samples that have less stringent exclusion criteria. The association between the GSS and sensory sensitivity has already been replicated in a female cohort (Manyukhina et al., 2021), and the neuroanatomy in autism has previously been extensively studied in both children and mixed sex samples (Ecker, 2017; Ecker et al., 2017; Opel et al., 2020; Postema et al., 2019). The aspect that is perhaps most lacking is regarding the specificity, since most studies (including ours) include single disorder case-control cohorts. In addition to the three-group methodology suggested above, it would be beneficial to include another NDD, such as ADHD or schizophrenia, in order to ascertain the specificity of the findings. The aspect of specificity is particularly important prior to the clinical implementation of classification methods, since there may be a considerable drop in performance when used outside of a case-control sample, such as for a pre-screened clinical sample (in particular for classifiers that implicitly rely more on features belonging to the NB/CC-complex).

# 7 IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

The operationalization of the pathogenetic triad can be used to implement personalized medicine through risk stratification, and the identification of individuals at risk that should be evaluated for a NDD. Furthermore, the proposed biological stratification using the operationalization of the triad could improve the detection of females and high-IQ individuals, for which the clinical interview has low sensitivity. Identification of NB/CC-complex dysfunction should prompt the evaluations of additional co-occurring NDDs in the proband, and any NDD in first-degree relatives (since such dysfunction is found at an increased rate in multiplex families).

The statistical method presented in Paper II represents a simple-to-use method for multivariable classification that can be applied also on other conditions and datasets. Its simplicity allows it to be used by clinicians and researchers without expertise in machine learning. The classification performed in that paper adds to a growing literature of classifying autism with accuracies in the same range as that of clinical evaluations.

With the development of cost-efficient and scalable classification methods that have replicable accuracies in other samples, they may start to be implemented clinically by supplementing the clinical evaluation. Although this thesis does not push the goal post that far, it argues for the importance of such development, where the main promise of automating the diagnostic process lies in allowing clinicians to increase their time spent treating patients.

The neurophysiological findings in Paper III show that the face processing of autistics is not notably different from neurotypical controls in the early post-stimulus period, at least in a normal-IQ sample, but that there may be divergent endophenotypes with regard to later periods. If this results from decreased experience due to lower social motivation or gaze aversion, it may serve to identify individuals where social communication training is more beneficial.

The marker of visual sensitivity identified in paper IV can potentially be used as a therapeutic biomarker in intervention studies. If the finding is replicated in younger samples, it could potentially allow for identification of visual sensitivity in pre- or non-verbal children. The marker may also extend to other domains, and be identified in areas such as the somatosensory cortex.

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- Stiftelsen Systrarna Greta Johansson och Brita Anderssons Minnesfond
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- Adlerbertska Stipendiestiftelsen
- Svenska Läkaresällskapet
- Svensk Förening för Medicinsk Radiologi and Siemens
- International Society for Autism Research

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