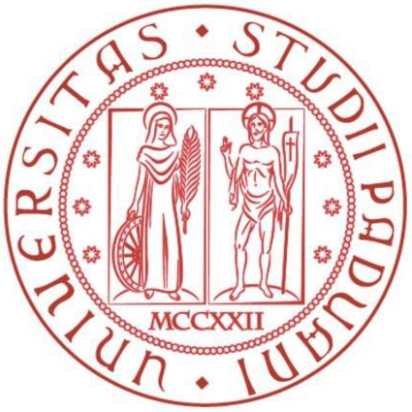

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TESI DI LAUREA

Retrospective study in patients with HF ASD and Asperger syndrome: observation on clinical phenotypes

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SUMMARY

Abstract in English

Autism spectrum disorder is a very heterogeneous condition, whose heterogeneity is in part determined by differences in intelligence quotient (IQ). This study focuses on the part of the spectrum without Intellectual disability (ID), which includes High Functioning Autism (HFA or HF ASD) and Asperger syndrome (AS). While “high functioning autism” is an unofficial expression used to describe autistic patients without intellectual deficiency (ID), the term “Asperger syndrome” had a brief existence as a diagnostic entity in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1995), before being removed in the fifth edition (DSM-5, 2013). Despite its short life span, Asperger syndrome still managed to arouse huge interest and controversy upon its diagnostic validity and its differentiation from HFA. The present study aims to examine AS and HFA and in particular their differences in clinical profiles. The population of the study was retrospectively collected among patients referred to the Neuropsychiatry Unit of Child and Woman Health Department, University Hospital of Padua, between January 2018 and January 2022. Forty-three patients, who received a diagnosis of autism spectrum disorder according to the DMS-5 criteria and who had no intellectual deficits, were selected. The patients were then divided into two groups based on the subtype: HFA and AS. Significant differences were found between the two, especially in the age of the patients at diagnosis, in many aspects of language and communication, as well as in comorbid disorders (anxiety and/or depressive disorders). No differences were found in many other aspects, such as motor and sensory systems, proving the strong similarity between the two subtypes. From a merely clinical point of view, similitudes appeared greater than differences.

Abstract in italiano

Il disturbo dello spettro autistico è una condizione molto eterogenea, la cui eterogeneità è in parte determinata dalle differenze nel quoziente intellettivo (QI). Questo studio si concentra sulla parte di spettro senza deficit intellettivo (DI), che comprende l'autismo ad alto funzionamento (HFA) e la sindrome di Asperger (AS). Mentre "autismo ad alto funzionamento" è un'espressione non ufficiale usata per descrivere i pazienti autistici senza deficit intellettivo, il termine "sindrome di Asperger" ha avuto una breve esistenza all'interno della quarta edizione del Manuale diagnostico e statistico dei disturbi mentali (DSM-IV, 1995), prima di essere rimosso nella quinta edizione (DSM-5, 2013). Nonostante la sua breve durata, la sindrome di Asperger è riuscita a suscitare un enorme interesse e diverse controversie sulla sua validità diagnostica e sulla sua differenziazione dall'autismo ad alto funzionamento. Il presente studio si propone di esaminare AS e HFA e in particolare le loro differenze nei profili clinici. La popolazione dello studio è stata raccolta retrospettivamente tra i pazienti afferiti all'Unità di Neuropsichiatria del Dipartimento di Salute del Bambino e della Donna dell'Azienda Ospedaliera Universitaria di Padova, tra gennaio 2018 e gennaio 2022. Sono stati selezionati 43 pazienti che hanno ricevuto una diagnosi di disturbo dello spettro autistico secondo i criteri del DMS-5 e che non presentavano disabilità intellettiva. I pazienti sono stati poi suddivisi in due gruppi in base all'appartenenza ai sottogruppi HFA e AS. Sono state riscontrate differenze significative tra i due soprattutto per quanto riguarda l'età dei pazienti alla diagnosi, molti aspetti del linguaggio e della comunicazione, e le comorbilità (disturbi ansiosi e/o depressivi). Non sono state riscontrate invece differenze in molti altri aspetti, come la motricità e il sistema sensoriale, a riprova della forte somiglianza tra i due sottotipi. Da un punto di vista meramente clinico, le somiglianze sono apparse maggiori delle differenze.

1. INTRODUCTION

1.1 History

The term “autism” originally comes from the Greek word "autos," meaning "self." It was first used in 1911 by the Swiss psychiatrist Eugen Bleuler. With this expression, he referred to one of the primary symptomatologic aspects of schizophrenia diagnosis: the individual's social withdrawal and isolation in his own world.

In 1943 the Austrian-American psychiatrist Leo Kanner identified autism disorder as a distinct neurological condition. Kanner studied a sample of eleven children who shared the trait of "closure in themselves", among other heterogeneous characteristics such as communication deficits, impaired social interaction, restricted, repetitive behaviors and interests. (1) (2)

In the same period (1944), Hans Asperger, an Austrian pediatrician, published a paper describing what he termed ‘‘autistic psychopathy’’ (3). His four patients had some, but not all, of the characteristics described by Leo Kanner: the core symptoms were the same, but generally in higher functioning individuals, with above-average intelligence and high-quality linguistic skills. Despite Kanner noticing that some of his patients, too, possessed good cognitive potential, Asperger referred to Kanner’s work stating that his subjects were clearly different from the ones analyzed by Kanner. (1)

1.1.1 Diagnostic criteria

In 1980 Kanner's syndrome was introduced as "Infantile Autism" in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) by the American Psychiatric Association (APA).

Asperger's publication, instead, as it was released in Germany during the Second World War and written in German, remained virtually unknown and did not enter the English-speaking medical community for many years.

Finally, in 1981, Lorna Wing, an English psychiatrist, published a paper that popularized Asperger's research, although renaming the disease ''Asperger syndrome'' (AS) to avoid the connotations of the term ''psychopathy''. Wing refined Asperger's initial set of diagnostic criteria and studied the similarities between the criteria proposed by Kanner and Asperger. In contraposition to the beliefs of Hans Asperger, she named the syndrome and Kanner's autism both part of an autistic continuum. (4)

The first diagnostic criteria for Asperger syndrome were proposed in 1988 by Carina and Christopher Gillberg. (5) According to them, AS diagnosis required six criteria based on Asperger's original case-reports: socially impairing egocentricity, restricted interests, obsessive routine adherence, unusual linguistic routines, deficits in non-verbal communication, and motor clumsiness. One year later, Szatmari and his colleagues proposed four mandatory criteria, comprising 22 symptoms: social isolation, impaired social functioning, deficits in non-verbal communication, and peculiarities of speech and language. (6)

In the 1990s, the syndrome was finally included in the 10th Revision of the International Classification of Diseases (ICD-10 by World Health Organization - WHO, 1992), and in the 4th version of DSM (DSM-IV - APA 1994) within Pervasive Developmental Disorders (PDD). DSM-IV's Pervasive Developmental Disorders had five subtypes:

- Autistic disorder (AD),
- Asperger syndrome (AS),

- Childhood disintegrative disorder (CDD),
- Pervasive developmental disorder-not otherwise specified (PDD-NOS),
- Rett syndrome.

Ever since, the definition of Asperger Syndrome and its boundaries with the subtype of Autistic disorder or PDD-NOS, associated with normal cognitive functioning, also known as High Functioning Autism (HFA or then HF ASD), has been the topic of a growing literature.

The expression “High Functioning Autism” was first used by DeMyer, Hingtgen and Jackson in 1981, to describe those children who had the classic signs of Kanner’s autism in their early childhood but, as they developed, exhibited stronger intellectual capacity, social and adaptive behavior abilities, and communication skills, than those typical of autistic individuals. (7) This expression has never entered DSM (or ICD), but it has been frequently used to describe PDD patients with average or above-average intellectual ability: Intelligence Quotient (IQ) higher than 70.

While researchers were focused on the development of measures with the ability to diagnose AS and differentiate it from HFA, the DSM-5 removed the diagnostic category of AS in 2013. In DSM-5, the identification of diagnostic categories has been superseded by the definition of the single broader category of autism spectrum disorder (ASD). This decision, which agrees with Wing's theories, was made for both scientific and socio-health reasons, to make more inclusive the access to enabling therapies. The World Health Organization (WHO) also followed a similar approach in ICD-11. (1) (4) (8)

1.1.1.1 PDD and AS according to DSM-IV (1995)

In DSM-IV (9) three categories of symptoms were considered, each of which included four symptomatologic manifestation modes.

I. Impairment of social reciprocity.

- Marked impairment in the use of various non-verbal behaviors, such as direct gaze, mimic expression, body postures, and gestures in social interaction.
- Inability to develop relationships with peers appropriate for development level.
- Lack of spontaneous attempts to share joys, interests, or goals with others.
- Lack of social or emotional reciprocity.

II. Language/communication impairment.

- Delay or total lack of development of spoken language (not accompanied by an attempt at compensation through alternative modes of communication).
- In patients with appropriate language, marked impairment of the ability to start or sustain a conversation with others.
- Use of stereotypical and repetitive language or eccentric language.
- Lack of various and spontaneous simulation games, or social imitation games.

III. Narrow and repetitive list of interests/activities:

- Absorbent dedication to one or more types of narrow and stereotypical abnormal interests or for intensity or focus.
- Completely rigid submission to unnecessary specific habits or rituals.
- Stereotypical and repetitive motor mannerisms.
- Persistent and excessive interest in parts of objects.

To make a diagnosis of PDD, at least six symptoms were required, with at least two in the first category (impairment of social reciprocity) and at least one in each of the other two categories.

To make a diagnosis of AS, at least two symptoms of social interaction impairment and at least one each from symptoms of communication and restricted, repetitive behavior were required, as well as normal cognitive and linguistic development before age 3. Furthermore, Autistic Disorder diagnostic criteria should not be met (otherwise, Autistic diagnosis should have precedence).

Thus, Asperger's syndrome contrasted with autistic disorder in:

- Absence of diagnostic criteria in the communication domain.
- Absence of necessity of onset before the age of 3.
- The addition of criteria regarding the absence of a language delay.
- The addition of criteria regarding the absence of deficits in cognitive development. (10)

As previously underlined, these criteria implied a differential diagnosis between AS and the other subgroup of PDD with normal cognitive functioning, namely HFA. The most controversial issues in AS versus HFA diagnosis appeared to be whether:

- Motor skills should be regarded as a differentiating feature.
- AS or HFA could be associated with cognitive disability.
- Language is impaired in HFA but spared, or even hyperfunctioning, in AS.
- A diagnosis of HFA and of AS can be made in the same person at different stages of development.
- HFA and AS refer to the same or distinct groups of individuals or are different conditions. (11)

1.1.1.2 ASD according to DSM-5 (2013)

The unsolved confusion in defining Asperger syndrome criteria and the clinical overlap between HFA and AS led to its merging into one unifying category with the fifth edition of DSM in 2013: autism spectrum disorder (ASD).

The main problem with DSM-IV was the priority given to the autism diagnosis: most individuals with major impairments in social interaction and limitations in interests and activities also meet the criteria for autistic disorder, precluding a diagnosis of AS. In addition, the criteria of normal cognitive and linguistic development failed to salvage the AS diagnosis because cognitive and linguistic delay is not required in order to identify autistic disorder (HFA) either. As Miller and Ozonoff demonstrated in 1997, even Hans Asperger's own first patients would fail to qualify for a DSM-IV diagnostic of AS. Moreover, it is sometimes impossible to verify retrospectively if a patient had normal language development before the age of three, and, in addition, full-scale IQ is rarely a helpful metric in AS, given the generally varied IQ profile. (12) For these reasons researchers have been using AS and HFA as interchangeable terms, compromising the possibility to compare various studies. Therefore, the latest edition of the DSM incorporated AS into autistic spectrum Disorder (ASD), removing the previously discrete diagnostic presentation of PDD.

With DSM-5, the categories of symptoms are reduced to only two:

- Persistent deficits in social communication and social interaction (which includes both social and communication difficulties).
- Restricted and repetitive behavior and/or interests and/or activities.

The diagnosis of ASD requires the presence of at least three symptoms in the category of "social communication deficits" and at least two in that of "repetitive behaviors". Important innovations introduced are the elimination of "language delay/impairment" among the symptoms necessary for diagnosis and the introduction of "unusual sensitivity to sensory stimuli" as symptomatology between "repetitive behaviors".

However, to better characterize the diagnosis and distinguish clinical profiles of ASD broader category, specifiers about language impairment, intellectual impairment and severity levels have been added.

According to the DSM-5, autism spectrum disorder must meet criteria A, B, C, D, and E:

"**A.** Persistent deficits in social communication and social interaction across multiple contexts [...]:

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 behaviors 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 in adjusting behavior 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 behavior, interests, or activities, as manifested by at least two of the following [...]

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 of verbal or nonverbal behavior (e.g. extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take the same route or eat the same 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 interests).

4. Hyper- or hypo-reactivity to sensory input or unusual interest 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 [...].” (13)

1.1.2.1 Autism level

In DSM-5, in addition to changes in diagnosis, autism levels are added (14).

1. Level 1 ASD is the least severe, it can be considered mild autism and requires minimum assistance to perform daily tasks. This level implies deficits in social communication and difficulty or less interest in social interactions. Level 1 autistic individuals may be able to talk in full phrases, however ordinary exchange of dialogue fails. Their attempts to establish friendships are uncommon. They frequently establish routines and are uncomfortable with changes or unplanned situations.

2. Level 2 ASD requires greater assistance Level 1 of autism.
   It implies marked deficits in verbal and non-verbal social communication and limited start and response in social interactions.
   Level 2 autistic individuals may or may not speak verbally; if they do, their talks may be brief or limited to a brief number of themes. They may also exhibit abnormal nonverbal behavior: not looking in the eyes or not

communicating their feelings in the same way most other individuals do, such as through tone of voice or facial expressions. Behavior inflexibility, trouble dealing with changes, or other restricted or repeated behaviors arise often and hinder operations in a variety of domains.

3. Level 3 ASD is the most severe form of ASD and requires very important support to learn skills that are necessary to perform daily life.
   It implies serious deficits in verbal and non-verbal social communication, a very limited start to social interactions, and minimal response to other people's overtures. These individuals may only know a few words, answer only to very direct social approaches and rarely start interactions. When they do, they use unusual approaches to meet their only needs. There is significant behavioral inflexibility, with extreme difficulties and frustration in dealing with changes, and other limited and repetitive habits substantially hindering functioning in all areas. They have restrictive or repetitive behaviors such as rocking, echolalia, spinning objects, or other activities.

Children with HF ASD and Asperger are often characterized by a level 1 of severity.

1.2. Epidemiology

The prevalence of autism spectrum disorder, including Asperger Syndrome, has been increasing over the years. This growth in prevalence rate has been attributed mostly to variables like changes in case definition, improved and more extensive screening, and higher awareness. Nevertheless, a real rise in the incidence of ASD is also plausible.
Various estimates of ASD prevalence have been recorded depending on the research population and methodology. Most investigations undertaken since the year 2000 in various geographical locations, by various teams, have converged on a median of 17/10 000 for AD and 62/10 000 for all PDDs combined (15). According to statistics from the Centers for Disease Control in Atlanta (CDC), the global prevalence of ASD in 2018 was 23.0 per 1000 children aged 8 years (one in 44 or 2,7%). (16)

In Italy the estimated prevalence ranges from 7.99 per 1000 (one in 125 or 0,8%) children according to the research by ASDEU (Autism Spectrum Disorders in the European Union) which examines children certified with ASD, up to about 11.5 per 1000 (one in 87 or 1,15%) children aged 7-9 years, according to a school screening study (17).

The frequency of Asperger's syndrome varies depending on the diagnostic criteria used. The American Psychiatric Association's DSM-IV and the WHO's ICD10 criteria are the most restrictive ones. The prevalence of Asperger's syndrome using DSM-IV or ICD criteria varies between studies, with reported rates ranging from 0.3 to 8.4 per 10 000 children (1 in 1200). According to the Gillberg criteria, the prevalence rate is higher, between 36 and 48 per 10 000 children (1 in 280 or 210). (7)
It is estimated that about 50% of AS children reach adulthood without ever being evaluated, diagnosed, or treated. (18)

1.2.1 Gender distribution

Regarding gender distribution, autism spectrum disorder is 4.2 times more common among boys than among girls (M:F=4.2:1) according to CDC (16). A meta-analysis shows that, in reality, this ratio is closer to 3:1 than to 4:1 because of a diagnostic gender bias: girls are more likely to go undiagnosed (19).

When talking about HFA and AS, the male-to-female ratio is even higher, ranging from 6:10 to 9:10 (20), and according to empirical data, high-functioning females are diagnosed later than males.

This suggests that females need more concurrent behavioral or cognitive problems, than males do, to be clinically diagnosed. The gender bias might be a result of behavioral criteria for autism or gender stereotypes and might reflect a better compensation or so-called “camouflage strategy” in females: girls typically have more elevated abilities to obtain social norms through a conscious effort of learning and adaptation.

Nevertheless, the male predominance is a consistent epidemiological finding that has etiological implications: female sex is associated with a higher disease threshold probably because of the presence of protection linked to genetic, epigenetic, and hormonal factors. (1) (4)

1.3. Etiology

The initial hypothesis on the etiology of autism was produced by Leo Kanner that blamed “cold" parenting, identifying autism as a relational problem (2). This hypothesis was carried forward until the 1970s through the psychodynamic theory of autism with the ideas of the "cold mother" and the "schizophrenic mother". In 1976, B. Bettelheim described autistic disorder as a defense strategy against a mother who did not have physical contact with her kid, as well as odd eating habits and communication issues (21).

The first neurobiological etiology concept was introduced by Goldstein in 1959: autism was defined as a defensive reaction to an organic defect (22). In 1964, B. Rimland reintroduced this notion, claiming the presence of organic morphological and functional deficits in this disease (23). However, the major protagonists in autism research and understanding were I. Lovaas and E. Schopler, authors of the behavioral idea. According to them, autism is a neurological condition with objective behavioral modes that may vary according to the interactions with the environment (24). Today, it is believed that the cause of ASD is multifactorial, with environmental and genetic components interacting, but the understanding of this interaction is still in its early stages.

1.3.1. Genetic factors

Despite the various etiological hypotheses for this complex disorder, the crucial importance of genetics in the etiology of autism was first recognized in the 1970s, when the first epidemiological studies on families and pairs of twins were conducted. Supports for the substantial genetic contribution to the development of ASD are: the detection of mutations and other DNA abnormalities in about 1/5 of cases (25), the strong role of inheritance in twins (monozygotic twins show a concordance rate for autism of 40-60% and for ASD of 70-90%, while dizygotic twins have much lower concordance: 0-20% (26)), the family recurrence risk and the unequal sex distribution with male predominance.

Family recurrence studies estimate that the risk rate in siblings of individuals with autism is 30-40 times higher than in the general population. Furthermore, family members of autistic people typically exhibit behavioral and cognitive features similar to those seen in the patient, but in a lesser form ("broader phenotype"). Excessive shyness, detachment and indifference in social contacts, anxiety, and restricted interests are all symptoms of a larger phenotypic that has nothing to do with mental retardation or epilepsy. (26) Even Hans Asperger observed similar traits in his patients' family members, particularly fathers (3).

Even though significant scientific data on the genetic foundation of autism exist, no clear model of inheritance or how environmental variables raise the risk of autism in genetically sensitive individuals exists. (26)

Nowadays there is rising evidence supporting a common genetic predisposition shared by neurodevelopmental diseases in general, rather than a particular genetic etiology for each illness. As a matter of fact, genetic investigations have found minimal support for the distinction between Asperger syndrome and Autistic disorder (27). On the other hand, there is a significant genetic overlap between ASD and other conditions such as epilepsy, intellectual disability, and schizophrenia. (28)

1.3.2. Environmental factors

The inability to explain all cases of ASD on a genetic basis has increased epidemiological research on environmental risk factors. A wide range of environmental factors have been found, but none of them have been demonstrated to be essential or sufficient on their own for autism to develop. The mechanisms of the association between environmental factors and ASD are debated but might include non-causative association (including confounding), gene-related impact, oxidative stress, inflammation, hypoxia/ischemia, endocrine disruption, neurotransmitter anomalies, and interference with signaling pathways.

Environmental risk factors for ASD can be divided into three categories:

1. Prenatal risk factors, concerning mental health, psychological health, and the financial state throughout the pregnancy. Among these factors it is important to highlight: parental reproductive age (especially paternal age), which has been identified as one of the most important risk factors of autism; maternal bleeding during pregnancy; metabolic syndrome, including diabetes, hypertension, and obesity, which paves the way for hypoxia in utero; maternal viral infections, such as Rubella and Cytomegalovirus, in the first trimester of pregnancy; prenatal exposure to chemicals such as valproic acid, pesticides, air and water pollutants, and heavy metals.
2. Natal risk factors such as abnormal gestational age, preterm (<35 weeks) and post-term pregnancy (>42 weeks); birth complications that are associated with trauma or ischemia and hypoxia; and caesarian section, which has shown a less strong (but significant) association with risk of ASD.
3. Postnatal risk factors such as low birth weight, jaundice, and postnatal infection. According to systematic reviews of multiple large epidemiologic studies, no evidence can support the popular beliefs of an association between ASD and immunization as an environmental risk factor; thus, children with ASD should be vaccinated according to the routine recommended schedule. (29) (30)

1.4. Neurophysiology

From a functional point of view, neurodevelopmental abnormalities occur in atypical neural networks with reduced long-range connectivity and excessive local connectivity. Moreover, an imbalance between neuronal excitation and inhibition has been hypothesized, which has been attributed to a variety of causes such as misalignment of inhibitory and excitatory synapses and paradoxical effects in which inhibitory neurotransmitters produce neuronal depolarization.

Functional MRI studies have revealed several anomalies in ASD patients:

- Reduced activation of the "social brain", that comprises the regions involved in the processing of social information: fusiform gyrus and amygdala.
- Abnormal fronto-striatal activation induced by cognitive control tasks and involved in stereotypies, obsessive-compulsive symptoms and repetitivity.
- During tasks involving the use of expressive language, a reduced left to right hemispheric lateralization, a lower synchrony of expressive language networks, with the involvement of regions that are not usually part of it.
- Anomalous responses to rewards of social and non-social nature, involving mesolimbic and meso-cortical circuits with anterior cingulate cortex, nucleus accumbens, amygdala and prefrontal ventromedial cortex.
- Reduced and abnormal activity of the operculum in the inferior frontal gyrus during observation and imitation tasks of other people's behaviors and emotional facial expressions. This impairment is linked to the functioning of "mirror neurons," which are necessary for the development of empathy and theory of mind.

Brain connectivity abnormalities documented by MRI have also been demonstrated by electrophysiological means, such as event-related evoked potentials. (1)

1.5. Neuropsychology

In the autism spectrum, some neuropsychological functions, that are important in the context of social cognition, are frequently compromised. Among these, there are three crucial functions that have been crucial in establishing contemporary perceptions of ASD's cognitive characteristics: the Theory of Mind (ToM), Weak Central Coherence (WCC) and Executive Functions (EF).

The theory of mind is the ability to understand the general mental state of the others and in particular their thoughts, beliefs, desires, and the purposes of their actions. (31) Compared to empathy, which can also be deficient in ASD, it is a more extensive concept, and, above all, it is more connected with cognition than with affectivity. Experimental evidence shows that people with autism performed worse on tests of ToM compared to age-matched and IQ-matched controls and in general perform poorly on activities that require them to portray the mental states of others. In addition, with the advent of fMRI, it was found that regions involved in the ToM perform less effectively and are less integrated in people with autism (*see section 1.4*).

It is important to notice that deficits in the theory of mind can explain defective social behavior in ASD, but it fails to account for the non-social symptoms of ASD, such as circumscribed interests, repetitive and stereotyped behavior and sensory anomalies.

Conscious of that, the researchers Happé and Frith proposed that autistic cognition was characterized by a detail-focused style of processing, which they called Weak Central Coherence (WCC). (32) Central coherence allows one person to balance attention to detail with attention to the complex stimulus. In the autistic subject, there is excessive attention to detail and marked difficulty in connecting different information or complex sensory stimuli in global visions. In ASD there is greater activation of the brain visual areas during visuospatial tasks, while in the controls there is greater activation of the frontal regions involved in executive functions and in the analysis of complex percepts. Enhanced ability in

perceptive discrimination may explain high intellectual talents and spectrum diversity.

The Executive Function theory offers a distinct account of cognition in ASD. Executive functions, essential for purposeful behavior, are often deficient in ASD patients and their families. They include the ability to plan a sequence of actions with a single purpose, the working memory, the capacity for self-control, and the mental flexibility in changing strategy if the chosen one does not lead to success. EF deficits are not specific to ASD, as they occur in many other conditions, such as acquired brain injury and attention-deficit/hyperactivity disorder. (1) (33)

1.6. Clinical phenotypes

ASD symptoms are neurologically based, but they appear as behavioral traits that vary depending on age, language ability, and cognitive skills. According to DSM-5 criteria, the core symptoms, common to the whole autism spectrum disorder, include impairments in social interaction and communication, as well as the presence of restricted and repetitive patterns of behavior, interests, or activities.
Abnormalities in understanding the purpose of others (ToM), reduced interactive eye contact, and atypical use and interpretation of gestures, suggest atypical development of social communication and pretend play as well as interest in other children. Symptoms of ASD are further shaped by deficits in imitation and processing information across sensory modalities, such as vision (gesture) and hearing (language). Repetitive behaviors and perseveration may be primary compulsions, but they may also indicate aberrant sensory processing or a desire to instill predictability when an individual does not fully comprehend the purpose of others. (34)
By convention, if an individual with ASD has an IQ in the normal range (higher than 70), they are said to have “high-functioning autism” (HF ASD). If an individual meets all of the criteria for HFA except communicative impairments or a history of language delay, they are said to have Asperger syndrome (AS). However, it is important to remind that HFA and AS are not recognized as proper entities by DSM-5.

1.6.1. Comparison between AS and HFA

Although there is a very significant overlap between AS and HFA, a review of 69 studies (1985-2010) found that some slight differences between AS and autism can be identified in terms of social interaction, motor skills, and speech patterns; moreover, all these aspects appear to be relevant for designing clinical and intervention strategies (35).

Tsai and Ghaziuddin in 2014 examined 125 comparative studies between AS and HFA (autistic disorder and PDD-NOS): 95 studies found quantitative and qualitative differences between them. The differences were more quantitative rather than qualitative, most of them regarding superior linguistic, cognitive, and social functioning. (36)

A 2018 Italian study by de Giambattista, Concetta et al., focused on the comparison between HFA and AS, suggesting that an AS empirical distinction within autism spectrum disorder should be clinically useful. (37)

According to literature, High functioning autistic patients are usually characterized by a higher performance IQ (PIQ) while Asperger patients have a distinct cognitive profile on intelligence tests with a typically high verbal IQ (VIQ) and a relatively low performance IQ (PIQ). (38) (39)

AS patients have typically no delay in language development (according to DSM-IV) and present an over-precise or pedantic speech, overly formal, verbose and tangential, often similar to an in-depth monologue about a topic of special interest, with the lack of the normal prosody (intonation, rhythm, tone). This “adult-like”, pedantic speech is one of the most typical clinical features of AS, firstly described by Asperger’s original work.

Although Asperger never provided details of any standardized intelligence tests or commented on the differences between VIQ and PIQ, he believed that his patients were gifted with high intelligence and that they had a special affinity for language, as they often developed their language skills before their ability to walk. Despite positive linguistic skills of AS, it is important to notice that they have specific difficulties, above all the inability to modify language according to the social context. (3) (7)

For what concerns HFA patients, they may have a language delay history and other language-related issues such as the literal interpretation of comments. (36) This last symptom might be connected to the HFA's lower cognitive and comprehension abilities, which make them unable to identify the speaker's communicative aim, in contrast to patients with AS who adopt intellectual

strategies of compensation (10). Nevertheless, this aspect is described also in AS children. (6)

Moreover, HFA patients appear more compromised in social and emotional abilities than AS ones, especially in avoiding social contact: while HFA children seem completely uninterested in others, AS children usually try to relate to others, but they do so in a dysfunctional way. The lack of social skills causes a higher risk of being a target of mockery by peers: more than 40% of children with ASD have been victims of bullying and intimidation at school.

Furthermore, AS individuals are characterized by exceptional long-term memory and are more fascinated by a specific topic compared to HFAs. Male Asperger's interests are usually means of transportation, science, electronics and computers, but also weapons, fire, pornography, and poisons. Female Asperger's interests are typically animals like horses and reading classics.

Comorbid disorders appear to be higher in AS than in HFA patients but, in general, HFA requires more support in terms of rehabilitative treatments and school educational needs than AS. Recent theories of neurodiversity started to consider AS a normal human difference rather than a pathological disorder. (10)

1.6.1.1. AS and gifted children

As Asperger children often possess above average intelligence, it can be challenging to distinguish an AS child from a child with "High Intellectual Potential" (HIP) or gifted child. HIP is defined by the threshold of IQ above 130. The difficulty lies in determining whether a child's unusual development is a result of giftedness, a learning disability, or AS. The differentiation is necessary to obtain appropriate assistance, because the social skills training that benefits AS children is different from the one that benefits children with other kinds of learning problems.

There seem to be about seven characteristics in common between gifted children and AS ones; these commonalities have not been verified in controlled studies, but are taken from shared literature and clinical experience. Both groups of

children are characterized by verbal fluency or precocity, excellent memories, fascination with letters or numbers, habit to memorizing factual information at an early age, absorbing interests in a specialized topic, hypersensitivity to sensory stimuli, irregular development particularly in social and affective competences at a young age.

Regarding distinguishing characteristics, they can mainly be found in speech patterns because AS children are usually pedantic, in rigidity about routines, because AS children have more difficulties coping with changes in schedules and procedures, and in inappropriate affective expression of AS children. Perhaps the most prominent feature to differentiate a gifted AS student from an only HIP one is the lack of insight and awareness regarding feelings, needs, and interests of other people, due to the lack of the theory of mind. AS children appear to be unaware of even the most basic social standards, and repeated attempts to teach or remind them have had no effect. (40)

However, HIP and ASD are not diagnostically mutually exclusive. A growing number of clinicians consider that an overlap exists between ASD and HIP, and emphasize the difficulty in assessing the presence of ASD in a child with a high Intellectual Quotient (IQ). These children are usually called “twice-exceptional” (“2e”) with reference to the association between a disability and high ability/giftedness. (41)

1.6.1.2 “Aspergirls”

As previously underlined, female Asperger girls can frequently go undiagnosed because of their apparent tendency to have less severe pathologic characteristics, with greater social skills and less aggressivity compared to their male counterparts. So called “Aspergirls” can be perceived by clinicians as someone who looks capable of developing a reciprocal discussion and is able to display suitable affectivity and gestures during the engagement. However, additional observations and investigations about their behavior at school are required,

because the mildness of their symptoms could be due to strategies they develop to acquire social skills, and coping mechanisms.

A strategy they use is to precisely “copy” someone who functions better: they can base their behavior persona on the traits of someone who is socially competent in the circumstance. They usually wait, observe carefully, and only participate when sure of what to do by imitating what children have done previously. If the rules or nature of the game suddenly change, these girls get lost. Moreover, Asperger’s girls are more likely than males to create a close friendship with someone who has a motherly attachment to this socially inexperienced but “safe” female. These qualities lower the chances of being detected as having one of the primary diagnostic criteria for AS, namely an inability to build peer interactions. It is not a failure with girls, but rather a fundamental gender difference in this skill. The girl's difficulties with social comprehension may only become apparent when her friend and mentor transfers to another school.

Another strategy that Girls with Asperger’s syndrome use is to “disappear” in a large group, being on the periphery of social interaction. They are usually well-behaved and polite and thus they are left alone by teachers and peers.

In general, these girls may have the same linguistic and cognitive profile as males, but their specific interests may not be as idiosyncratic or eccentric as some guys. They are frequently interested in animals like horses, reading classics - from which they can learn social strategies - or playing with dolls, useful to practice social competencies. The problem may be the intensity and dominance of these interests in daily life.

It is not uncommon for aspergirl to come to clinicians’ attention with eating disorders, such as anorexia nervosa or gender dysphoria.

It is important to notice that due to the severe social naivety of these girls a risk of sexual abuse might exist. This is because of their inability to recognize socially evident, in particular non-verbal, messages of sexual invitations. (7) (42)

1.7. Comorbidities

Co-existence with other mental and physical illnesses is common in the autism spectrum, especially in young children. This might have a significant impact on the patient and their family, as well as on clinical care.

ASD frequently occurs in combination with other neurodevelopmental disorders such as Intellectual Disability (40-69%) (43), Attention Deficit Hyperactivity Disorder - ADHD (33-37%), Specific Learning Disorders and Developmental Coordination Disorder (30-40%), as well as psychiatric disorders including anxiety disorders (39.6%), mood disorders, and Obsessive-Compulsive Disorders (17.4%). Moreover, ASD patients can have comorbidity with neurological illnesses, particularly epilepsy, which occurs in about 5-10% of high-functioning patients and about 20-30% of low-functioning patients. EEG abnormalities without epileptic seizures are very common (35-65%), indicating that an EEG might be informative. (1)

The average or above-average cognitive functioning ASD subpopulations, AS and HFA, are commonly more associated with ADHD, depression and anxiety, bipolar disorders, and tic disorders. (10) In these patients, clinicians may struggle to identify psychiatric comorbidities because these individuals may have difficulties interpreting and communicating their own experiences and emotions. Furthermore, the symptoms of psychopathological illnesses may be hidden by AS/HFA specific symptoms.

The most frequent in both subtypes is typically ADHD, the most common mental condition in children and teenagers. According to studies, several symptoms overlap in ADHD and AS. As such, AS should be considered when diagnosing ADHD with severe interpersonal problems. A drop in attention level may be caused by high distractibility in ADHD and a lack of mental flexibility in AS. Additionally, both diseases may pose challenges in interpersonal relationships, and both may hyperfocus in engaging in their hobbies.

When comparing Asperger Syndrome and High Functioning Autism, comorbid disorders appear significantly higher in AS than HFA, especially anxiety and

depressive disorders. (9) Countless triggers can take these patients to anxiety disorders: unpredictability, routine changes, sensory experiences, etc. This comorbidity may be the foundation of school retreat and, in extreme cases, might also lead to delusions and loss of contact with reality.

Different triggers can also cause depression: feeling different, mental exhaustion, bullying, low self-esteem, isolation, etc. According to a 2014 study, 66% of Asperger's individuals contemplated suicide and 35% attempted it. (44) (45)

1.8. Diagnosis

1.8.1. Onset and recognition

Signs of autism are not reliably present at birth, but emerge through a process of diminishing, delayed, or atypical development of social-communication behaviors, starting between the ages of 6 and 12 months. Early identification allows early intervention; therefore, it is important to identify early indicators. Among early indicators there are anomalies or delays in the emergence of joint attention and pretend play, atypical implicit perspective talking, deficits in reciprocal affective behavior, decreased response to own name, decreased imitation, delayed verbal and nonverbal communication, motor delay, unusually repetitive behaviors, atypical visuomotor exploration, inflexibility in disengaging visual attention, and extreme variation in temperament. (4)

Parents or caregivers of children with ASDs generally identify early indicators and concerns by the age of 12 to 18 months. This is valid for both AD and PDD-NOS, but not for Asperger individuals, that would rarely be diagnosed at 2 years of age. (46) As a matter of fact, among 24 studies reporting the age at diagnosis for autistic disorder, median ages was about 3 to 7 years; while among 16 studies reporting the age at diagnosis for Asperger's syndrome, median ages ranged from about 7 to 10 years. (47)

Thus, the recognition of autistic children without cognitive deficits, especially Asperger ones, generally happens later than lower functioning ASD children. This is attributed to the relatively more preserved language (Asperger syndrome criteria include language skills at 33 months) and cognitive abilities. Frequently, these children may not be identified until school age, when differences in social language or personal rigidities affect function. Many AS adults who are diagnosed in their adulthood state that the first time they felt different from others was when they started school. They describe being able to understand and relate to family members, but when they were expected to interact with their peers at school,

they recognized themselves as being very different: not interested in social activities of their peers, not wanting to include others in their own activities, and not understanding the social conventions in the playground or classroom. (48)

In general, it is important to notice that the average age at diagnosis for all autism spectrum disorders, according to a review of 42 studies (1990-2012), has been identified between 3 to 12 years, with a downward trend over time. Autistic children are diagnosed earlier and earlier in years and this could be ascribed to greater symptoms severity, higher socioeconomic level of population and abundance of parental awareness and worry over first symptoms. (47)

1.8.2. Diagnostic process

The lack of specific biological markers for the identification of autism disorders demands a diagnosis based only on behavioral factors. As a result, precise anamnesis, meticulous clinical observation, and the use of standardized evaluation methods are all required.

The evaluation should be conducted with careful consideration of diagnostic criteria according to DSM-5. Attention to other potential comorbid diagnoses is also an essential component of the examination. Co-occurring conditions may impact the symptomatology of ASD in various ways and at different ages of life.

The diagnostic process starts with the anamnesis, which should cover gestational, birth, developmental, and health history, as well as family medical and psychiatric history. The family history should include questions about any family members who may have a similar pattern of abilities, but not necessarily a diagnosis of ASD. It is also important to remember that there is a high risk of recurrence of ASD in siblings.

Afterward, an objective exam is necessary, including a general objective exam, a neurological exam and a psychiatric exam. An experienced clinician needs to assess the domains of social reasoning, communication of emotions, language and cognitive abilities, interests, movement and coordination skills, as well as examine

aspects of sensory perception and self-care skills. The diagnostic evaluation should look not just at areas of difficulty, but also at areas of ability that may be related to Asperger's syndrome features. Some individuals are quite simple to diagnose and a clinician may assume a diagnosis within minutes. About AS patients, Hans Asperger said: “One can spot such children instantly. They are recognizable from small details, for instance, the way they enter the consulting room at their first visit, their behavior in the first few moments and the first words they utter.” (3). However, full diagnostic assessment has to be done to confirm the initial clinical hypothesis.

Tests and questionnaires can be very helpful, even if the findings of the tests might not always concur with the specialist's assessment. The two specific diagnostic scales that can be used to analyze the presence and severity of the symptoms of the autism spectrum disorder are the Autism Diagnostic Interview (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). (34)

It is important to underline that these tools tend to have a lower sensibility to assess individuals with higher IQ: HFA and AS. (49) Thus, in these patients it is helpful to add the use of other specific tests and questionnaires such as ASDI (Asperger Syndrome and High-Functioning Autism Diagnostic Interview) by Gillberg and colleagues (2001), KADI (Krug Asperger’s Disorder Index) by Krug and Arick (2002), ASAS (Australian Scale for Asperger Syndrome) by Attwood (2006), and the tools provided by the Autism Research Centre of the University of Cambridge.

Possibly, in addition to the clinical context, it would be desirable to include differentiated observation settings for a more complete collection of information (eg observations of the child at school and at home). It is not often possible to observe the patient directly in these areas, but it is possible to use video recordings brought by the caregivers. (1) (50)

1.8.2.1. Medical insights

Along with purely clinical diagnosis, laboratory analysis and instrumental diagnostics are also used as complements. Various organic investigations are indicated within the evaluation protocol, including laboratory blood tests, such as thyroid profile, celiac screening, iron, vitamin profile (which is suggested also for the high incidence of food selectivity in ASD children), as well as urine analysis. Further possible investigations are neurophysiological examinations, such as electroencephalogram (EEG), and radiological examinations, such as magnetic resonance imaging (MRI).

The EEG is performed because epilepsy and autism spectrum disorders frequently coexist in the same individual. Epileptiform activities on EEG are also present to a substantially higher extent in children with autism than in normally developing ones.

The MRI is not recommended for regular evaluation, it may be necessary in the case of aberrant regression, micro- or macrocephaly, seizures, or abnormal neurologic examination. (50)

As part of the etiologic assessment, providers should also propose and offer a genetic examination to all families. Identifying a genetic etiology provides clinicians with more information for families about prognosis and recurrence risk and may help to identify and treat or prevent co-occurring medical conditions, guide patients and families to condition-specific resources and supports, and avoid ordering unnecessary tests. (34)

1.9. Tests

1.9.1 Screening tests

Screening tests are used in the context of primary care to aid early diagnosis. They do not provide a diagnosis, but they can suggest if a kid is on the appropriate developmental path or whether an expert should be consulted. If the tool identifies areas of concern, a formal specialistic developmental evaluation may be needed. Some of these screening tests are:

- **M-CHAT-R/F**, a 20-item parent-completed questionnaire designed to identify children at risk for autism younger than 30 months of age, which can be also used as a follow-up by clinicians.
- **SCQ** Social Communication Questionnaire (Rutter et a., 2003), a 40-item, true/false, parent-completed questionnaire that is based on items in the ADI-R. It is used as a brief screening to determine the necessity to conduct a complete ADI-R interview. There are two types of SCQ: “Life span” and “Last three months”. The latter version can be very useful for the evaluation of current treatment and of the educational projects the patient has undertaken.
- **STAT**, a 12-item, interactive and observation measure, that requires the training of a specialist for standardized administration. Differently from the other two tests, it is not for population screening. (34) This test was not used in the patients of this study, because it is not generally employed in the Neuropsychiatric Unit of the Neuropsychiatry Unit of the University Hospital of Padua.

1.9.2 Diagnostic assessment tests

Once a child is determined to be at risk for a diagnosis of ASD, a timely referral for clinical diagnostic evaluation and early intervention or school services, according to his or her age, is indicated.

Measures such as the Behavior Assessment System for Children, Diagnostic Interview for Social and Communication Disorders (DISCO), and Child Behavior Checklist (CBCL) are used to assess children and youth for other behavioral health conditions but may also identify behavioral profiles consistent with ASD. (34)
As already stated, the two specific diagnostic scales that are used to diagnose Autism Spectrum Disorder are ADI-R and ADOS.

1.9.2.1. ADI-R (Autism Diagnostic Interview)

ADI-R is a lengthy, semi-structured interview of 93 questions administered to the caregivers of the patients, useful for obtaining a wide range of information focusing on three domains: reciprocal social interaction, language and communication, and patterns of behavior, with particular attention to repetitive and stereotyped behavior and the breadth of the subject's repertoire of interests of the individual.
It supports a knowledgeable clinician in applying diagnostic criteria of ASD.
The SCQ was designed to elicit similar information to the ADI-R in an abbreviated questionnaire format. (51)

1.9.2.2. ADOS (Autism Diagnostic Observation Schedule)

ADOS is a standardized diagnostic test for Autism Spectrum Disorder. It consists of a series of pre-established activities during which the examiner detects the behaviors deemed crucial for a diagnosis of ASD.
The original edition of ADOS (ADOS-1) comprehends four separate modules. The choice of the module is based on chronological age and language level of the patients:

- Module 1: for individuals who struggle with verbal communication. Make use of just nonverbal scoring possibilities. It can be used for patients from 31 months of age.

- Module 2: for individuals with limited verbal communication abilities (language with sentences but without a true verbal fluency). The majority of scenarios include moving around the area and interacting with items.
- Module 3: for individuals who speak fluently and can play with age-appropriate toys (usually under 12-16 years of age).
- Module 4: for individuals who speak fluently, but are over the age of the game (adolescents and adults). It includes certain parts from Module 3 as well as additional conversational features about ordinary life situations.

The new ADOS-2 version is characterized by the introduction of a new module, the Toddler Module, which can be administered even to 12 months old children (from 12 to 30 months). Differently from the other modules, it provides a risk indicator and not a cut-off.

The examiner must write very detailed notes during the administration of the tests and the coding should take place immediately after administration. Every module can be compiled in 40 minutes. (52)

1.9.2.3. CBCL (Child behavior checklist)

CBCL is one of the most used child behavior assessments in epidemiological international studies and clinical practice. In ASD patient CBCL can be useful do examine comorbidities. There are two versions depending on the age of the child: 1 1⁄2 to 5 years (pre-school) - 100 items (Achenbach & Rescorla, 2000) and 6 to 18 years (school age) - 118 items (Achenbach & Rescorla, 2001; Frigerio et al., 2004). Alternative questionnaires are available for teachers (Teacher's Report Form) and the child (Youth Self Report, for 11 to 18 years old children). Parents are asked to answer each item and fill in the questionnaire thinking about their child's behavior in the current state or in the last six months, indicating the truthfulness of each statement, on a three-point scale (0 = not true, 1 = sometimes true, 2 = very true). Scoring allows to identify “Syndromic scales” and “DSM Oriented scales” that guide the clinician towards the formulation of a diagnostic hypothesis according to DSM.

The eight Syndromic scales comprehend anxiety and depression, withdrawal and depression, somatic complaints, social problems, thought problems, attention problems, aggressive and breaking rules behaviors. In the preschool version the scale of emotionally reactive and problems of sleep are also added. These scales are grouped in two dimensions: internalizing and externalizing behavior problems. The DSM Oriented scales, on the other hand, include affective problems, anxiety, somatic problems, attention deficit hyperactivity disorder, oppositional defiant disorder, conduct problems and pervasive developmental disorders for preschoolers.

The scores of normal children of the same age can be compared with the assessed child. Scores are classified as normal, borderline, or clinical. (53)

1.9.3 Specific tests for Asperger syndrome and High Functioning ASD

- **ASDI** or Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview (Gillberg et al. 2001). It is a 20 items questionnaire based on the criteria of Gillberg and Gillberg. (54)
- **ASDS** or Asperger Syndrome Diagnostic Scale (Myles, Bock and Simpson 2001).
- **CAST** or Childhood Asperger Syndrome Test (Scott et al. 2002; Williams etal. 2005), screening test developed to identify children at risk for the Asperger's syndrome within a non-clinical group (5-11 years old). It can be also used in the clinical setting as a completion of the assessment when an autism spectrum disorder with mild support need is suspected and a referral to a specialist is planned.
- **GADS** or Gilliam Asperger Disorder Scale (Gilliam 2002), applicable for individuals from 3 to 22 years old.
- **KADI** or Krug Asperger's Disorder Index (Krug and Arick 2002), applicable for individuals from 6 to 21 years old.

- **ASAS** or Australian Scale for Asperger Syndrome (Attwood 2006), a questionnaire for childhood with 5 domains (social-emotional abilities, communication skills, cognitive skills, specific interests, movement skills) and "other characteristics" (presence/absence of atypical sensitivity, stereotypic movements and language delay). It does not have a cut-off score, but it's used for clinical purposes.
- **GQ-ASC** or Girls' Questionnaire for Asperger Syndrome (Attwood & Garnett, 2013). It has three indicators: game, friendship, and social situations, abilities and interests.
- **MASQ** or Michigan Autism Spectrum Questionnaire (Ghaziuddin and Welch et al. 2013) is a questionnaire in which the highest total scores (>22) predict Asperger syndrome, the intermediate scores (14 through 21) predict HFA, and the lowest scores (<14) predict other psychiatric disorders. (55)

1.9.4 Other tests

1.9.4.1 PSI (Parenting stress index)

PSI (by Abidin, 1995) is a self-report questionnaire to assess the perception of parental stress. To address the need for a psychometrically sound but brief screening, Abidin developed a 36-item PSI–Short Form (PSI–SF). It asks the parent to indicate the degree of agreement for each statement (FA = strongly agree, A = agree, I = not sure, D = disagree, FD = strongly disagree). The subscales investigated comprehend: Parental Distress (PD) which describes the level of parental stress related to personal factors; Dysfunctional Parent-Child Interaction (P-CDI) which analyzes the quality of the relationship with the child; Difficult Child (DC) which analyzes the traits of the kid; Total Stress which is an overall measure of the parenting stress; Defensive response (DR) which indicates the presence of a

defensive attitude of the parents who can deny or minimize the potential stressors in the relationship with the child. (56)

1.9.4.2 ARC tests

Autism Research Center - a group of researchers of the University of Cambridge - provides a series of freely available tests and questionnaires useful for the evaluation of ASD patients, and in particular high functioning ones, but not diagnostic. Some of these tests are:

- AQ Test for children or adolescents (Baron-Cohen et coll., 2008).
- Face Test for Children (Baron-Cohen et coll., 2004).
- Eye Test for Children (Baron-Cohen et coll., 2001).
- Empathy Quotient for Children (Baron-Cohen et al, 2010).
- Friendship Quotient (Baron-Cohen and S. Wheelwright, 2003).
- Social stories. (57)

1.10. Evaluation of neuropsychological profile

The neuropsychological assessment aims to investigate the basic neuropsychological functions such as cognitive level, memory, attention, perception, language, visual-motor integration, executive functions and theory of mind. The choice of the tools depends on the child's characteristics: chronological age, verbal-communication skills, abilities to respond to complex tasks and to interact socially. (50)

1.10.1 Cognitive profile

1.10.1.1. Wechsler Scales

The Wechsler Scales are the most extensively used worldwide tests for assessing Intelligence Quotient (IQ). It is important to underline that IQ tests' scores reflect an ordinal scale. The raw score of the norming sample is usually (rank order) converted to a normal distribution with a mean of 100 and a standard deviation of 15. While one standard deviation equals 15 points, two standard deviations equal 30 points, and so on, this does not imply that mental capacity is directly proportional to IQ, such that IQ 50 equals half the cognitive ability of IQ 100. IQ scores, in particular, are not percentage points.

There are three versions of Whechsler Scales, one for each age group: the Weschler Preschool and Primary Intelligence Scale (WPPSI-III) for children aged 2.6 to 7.3 years; the Weschler Intelligence Scale for Children (WISC-IV) for children and adolescents aged 6-16 years and 11 months; and the Weschler Adult Intelligence Scale (WAIS-IV) for adolescents and adults aged 16 to 90 years. (55)

WISC (Wechsler Intelligence Scale for Children)

WISC (by Wechsler, 2014) is a clinical and diagnostic tool for the evaluation of the intellectual abilities of children from 6 to 16 years and 11 months, with the peculiarity that it is not necessary to know how to read or write to undergo the

test. The administration of the test takes about 70 minutes. The WISC III and IV versions were used for the evaluation of patients included in the study.

The WISC III is a scale composed of 13 subtests divided into two groups: verbal subtests and performance subtests. The administration takes place by alternating a test of the verbal scale with a test of the performance scale. Subtests select different mental abilities (memory, abstract reasoning, perception, etc.) that altogether contribute to the general intellectual ability (IQ), which is expressed through 3 scores: verbal IQ (QIV), Performance IQ (QIP), Total IQ (QIT). The latter is a combination of QIV and QIP.

The WISC IV, on the other hand, consists of 15 subtests, of which 10 are fundamental and 5 additional. In particular, 3 of the main subtests of the WISC III version have been deleted and 5 new subtests have been added instead. The 15 subtests allow the computation of a general composite score (IQ) and four partial scores that evaluate specific cognitive domains: Verbal Comprehension Index (ICV), Visual Perceptual Reasoning Index (IPR), Working Memory Index (IML), Processing Speed Index (IVE). The most recent version of WISC is the 2014 WISC-V. (55) (58)

WPPSI III (Weschler Preschool and Primary Intelligence Scale)

WPPSI III (by Lichtenberger, 2006) was born to bypass the limits of applicability of WISC to less than 6 years of age. It consists of 14 subtests: 7 verbal, 5 performance, and 2 processing speeds. (55) (59)

1.10.1.2 Leiter International Performance Scale Revised (Leiter-R)

Leiter-R is another useful tool to access cognitive profile. It is a test that measure the intelligence and nonverbal abilities of patients between the ages of 2 years and 20 years and 11 months. It consists of 20 subtests. The first 10 subtests - “Visualization and Reasoning” battery (VR) - measure traditional intelligence constructs (reasoning, visualization, troubleshooting) and allow to get two IQ scores (one calculated on the full IQ scale and one on the short IQ scale).

The other 10 subtests - “Attention and Memory” battery (AM) - evaluate attention and memory. (55) (60)

1.10.1.3 Raven's progressive matrices

Raven matrices (by Raven 1938) are a test for measuring non-verbal intelligence that can be administered to people of all ages, regardless of cultural level. In each card the patient is asked to complete a series of figures with the missing one. Each group of items becomes more and more difficult. Raven's matrices are considered the elective test for measuring intelligence defined as fluid. (55)

1.10.2 Adaptive profile

Adaptive behaviors are typically delayed in ASD patients who have intellectual disability but can be impaired also in people with ASD and an average-range IQ. (61) Commonly used adaptive measures include the Vineland Adaptive Behavior Scales and the Adaptive Behavior Assessment System.

1.10.2.1 The Vineland Adaptive Behavior Scales (VABS)

The Vineland Scales are used to assess the activities that a person, aged 0 to 90, habitually carries out to meet the expectations of personal autonomy and social responsibility for his or her peers of age and cultural context. They are designed to measure adaptive behavior in the domains of socialization, communication, motor skills, and daily living skills. The acquisition of normal developmental landmarks is assessed from infancy to adolescence. High scores indicate greater adaptability, but is unknown how much scores must change for those changes to be regarded as clinically significant. Recent versions of Vineland are Vineland II, published in 2005, used for this studio, and Vineland-3, in 2016. (55)

1.11 Treatment

Treatment options for individuals with ASD may differ depending on patient age, strengths, limitations, and requirements, as well as the mode of administration and intervention aims.

Although autism is rooted in biology, most effective interventions so far are behavioral and educational; drugs have had only a minor role.

The objective of these treatments is to reduce fundamental impairments, increase functional independence, and reduce problematic behaviors that may limit functional skills. (62)

Early diagnosis and early intensive treatment can improve patients' outcomes. As a matter of fact, although there is no cure, symptoms can decrease over time and, in a few cases, they are so minimized that they no longer cause disability.

Regarding AS patients, the advantage of having a diagnosis is not only in preventing or reducing the effects of some compensatory or adjustment strategies, but also in removing worries about other diagnoses and giving them a sense of identity and a relief in feeling recognized in their own characteristics. (7)

The self-knowledge resulting from a diagnosis can make it possible to comprehend certain past failures and to be better able to adapt to present situations, and even to recognize the situations to be avoided. Similarly, parents will have a better understanding of the development and the academic and social careers of their child, usually entailing a reduction in their guilt feelings. (63)

With a diagnosis, it is also possible to introduce children to support groups, encouraging them to make connections with people who have similar characteristics, and thus helping them feel understood.

1.11.1. Behavioral Interventions

According to a review published in The Lancet (2014), the different behavioral approaches can be classified into five complementary categories, described below.

1. **Early Intensive Behavioral Intervention (EIBI)**. Eclectic approaches that aim at the rehabilitation of different skills (cognitive level, language, sensorimotor skills and adaptive skills) through intensive long-term programs. This category includes structured learning approaches such as Applied Behavior Analysis (ABA) and the Early Start Denver Model (ESDM). EIBI approaches are generally aimed at preschool children.

   ABA is a process of intensive behavioral interventions aimed to teach new skills and generalize learned skills by breaking them down into their simpler elements. These skills are taught through trials and rewards. ABA is usually home-based or school-based with a 1:1 adult-to-child ratio and intensive teaching for 20–40 h/week, for 1–4 years.
2. **Treatment and Education of Autistic and related communication Handicapped Children (TEACCH)**. The TEACCH method aims to develop the greatest possible degree of autonomy in personal, social and working life, through educational strategies that enhance the abilities of the person with ASD.
3. **Interventions aimed at specific target-skills**, such as, language (Picture Exchange Communication System, PECS), social skills (Social Skill Training) or autonomy (Training in living skills and autonomy). These treatments are useful for children, adolescents, or adults who have unique assistance requirements in certain areas.
4. **Cognitive-behavioral therapy (CBT)**. It represents the target intervention methodology for comorbid aspects such as anxiety and aggression. CBT's theoretical background presumes that pathologic anxiety is the result of an interaction between excessive physiological arousal, cognitive distortions and avoidance behavior. As a result, the fundamental

components of CBT involve training emotional regulation skills to reduce physiologic arousal and maladaptive thinking, followed by systematic exposure to fearful circumstances to reduce avoidant behavior and develop personal coping strategies that target solving current problems.

5. **Parent-mediated interventions** aimed primarily at preschool children. They teach to parents or caregivers intervention strategies that can be applied in home and community settings, potentially increasing parental efficacy and enabling child's generalisation of skills to real-life settings. (4)

1.11.2. Pharmacologic Interventions

Only two medications have been authorized by the US Food and Drug Administration (FDA) for the treatment of ASD symptoms: Risperidone and Aripiprazole. They are used in the short term to treat psychiatric comorbidities such as aggressiveness, self-injury, and irritability, but not to cure major deficits. Risperidone and Aripiprazole can be used in ASD children from the ages of 5 and 6 years, respectively. (10) (64) Potential adverse effects include weight gain, sedation, extrapyramidal symptoms, and hyperprolactinaemia (risperidone). (4)

1.11.3. HFA and AS educational interventions

Social impairment in autism is shared: it is experienced by ASD people and those who live and work alongside them. An individual with HFA/AS may be confused or overwhelmed by specific social situations and interactions and, at the same time, parents and professionals may view the responses of the person with HFA/AS as "inappropriate", "without apparent reason." Consequently, improving social interactions necessitates techniques that address both sides of the social equation. Among these, there are "Social Stories" and "Comic Strip Conversations" by Carol Gray.

A Social Story is a brief description of a certain circumstance, event, or activity that offers detailed information about what to expect and why. They can provide an individual a notion of how others would react in a certain scenario, and therefore provide a framework for proper behavior. Social Stories can allow people to view things through the eyes of the person with ASD and why the person appears to respond or behave in a certain manner.

Comic Strip Conversations (CSCs) use symbols, stick figure drawings, and color to depict the many levels of communication that occur throughout a conversation. Some of the abstract parts of social communication (for example, understanding the sentiments and intentions of others) are made more real and hence simpler to grasp by graphically presenting the various pieces of a discussion. CSCs can also give insight into an ASD individual's view of a certain circumstance. (65)

1.12. Prognosis

The outcome of ASD patients is associated with cognitive gain and improved adaptive functioning during development. (4) Approximately 9% of children who are diagnosed with ASD in early childhood may not meet the diagnostic criteria for ASD by young adulthood.

Even if prognosis and development trajectory for a young ASD child cannot be predicted at the time of diagnosis, there are several factors that appear to be related to prognosis.

Actually, youth who no longer meet criteria for ASD are more likely to have a history of higher cognitive skills at 2 years of age, to have participated in earlier intervention services, and to have demonstrated a decrease in their repetitive behaviors over time.

On the other hand, ASD children with language impairment and intelligence disability appear to have more social difficulties compared to patients without language and cognitive disabilities. Thus, measured intelligence and language ability in childhood tend to predict outcome in adulthood.

In high-functioning adults with ASD, reported quality of life was associated more with the presence of family and community supports than their symptoms related to ASD. (34)

Another prognostic factor can be found in the presence or absence of comorbidities. A meta-analysis showed that individuals with autism have a mortality risk that is 2.8 times higher than that of unaffected people of the same age and sex, and this difference is precisely mostly related to co-occurring medical conditions. (4) (66)

2. STUDY MODEL

2.1 Purposes

The purpose of the study is to analyze the existence of differences in subpopulations of patients with a DSM-5 diagnosis of autism spectrum disorder (ASD). In particular, the study focuses on the high functioning part of the spectrum, which encompasses patients with average or above average Intelligence Quotient (IQ>70), namely High Functioning Autism (HFA) and Asperger Disorder (AS).

The choice of this purpose is linked to the recent merger of DSM-IV category of Asperger syndrome in the DSM-5 broader diagnostic category of ASD. The study reflects upon the utility and the clinical reliability of this decision. With this purpose, we examined whether subjects with AS differ from other subjects with autism spectrum disorder, and in particular with the patients with a similar IQ level to AS, namely high functioning autistics (HFA). Moreover, if they are present, the study examines whether these differences are more qualitative or quantitative. Where there are no differences, the study aims to describe the common characteristics of these part of autistic spectrum.

2.2 Participants

The population of this study was retrospectively collected among patients referred to the Neuropsychiatry Unit of Child and Woman Health Department of the University Hospital of Padua, between January 2018 and the end of January 2022. In this 4-years-period, 144 children who received a diagnosis of autism spectrum disorder (ASD), were visited. The diagnosis of ASD was made according to the DSM-5 criteria (13), expert clinical judgment, and scores from gold standard diagnostic tools: the Autism Diagnostic Interview Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS) and other complementary tools (see

section 1.9). These patients include 114 males and 30 females with a male-to-female ratio of 3.8:1, and this data agrees with the gender distribution of ASD that can be found in the literature (19). The mean age of all patients at the moment of the evaluation was approximately 4.7 years old (excluding 2 patients with a high age at diagnosis: 16 and 17). If we exclude high functioning patients (AS and HF ASD), the mean age at diagnosis drops to about 3 years old.

Among the 144 patients, 43 individuals who had normal or above average cognitive functioning (Intelligent Quotient higher than 70), were selected for the study. The IQ of the patients was assessed using neuropsychological tests or, in absence of administered tests, clinical assessment. In particular, Wechsler Scales were the most used for the evaluation of the IQ of the patients in the study: WISC in 24 patients, WPPSI-III in 4 patients. Other administered tests were Raven Matrices in 1 patient and Leiter-III in 1 patient.
Therefore, inclusion criteria of this study are a clinical diagnosis of ASD, according to DSM-5 criteria (APA 2013) and Intelligent Quotient average or above.
All patients with a proven or suspected intelligence disability were excluded from the selection. Patients with too little or indeterminate data were also excluded.

The 43 patients considered include 38 males (88.4%) and 5 females (11.6%), with a male-female ratio of M:F= 7.6:1. The higher male to female rate of this higher functioning individuals agrees with the different gender incidence of HFA and AS patients described in literature (20). The average age of the sample at the moment of the evaluation is 8.81 years (±4.31).

More than ninety-five percent of the selected patients had a level 1 of severity by DSM-5 (people who require minimal support), and only 2 HF ASD patients were specified to have a level 2 of severity (people who require substantial support in some areas), representing the general less severity of the high funcioning part of autistic spectrum.

3. MATERIALS AND METHODS

3.1 Materials

The data were collected through a study of medical records, both computerized and on paper. The examined documents contained reports of visits and outpatient consultations, as well as the most important tests given to the patients.

For each patient, the following variables were gathered:

1. Anamnestic data: family history, obstetric anamnesis, physiological anamnesis, language and psychomotor development, social smile and pointing, pathological anamnesis, comorbidities.
2. Free observations data: room exploration, gaze and facial mimics, language and communication, play, restricted interests, imitation, stereotypes, frustration tolerance, motricity, and other aspects.
3. Medical records: laboratory exams, EEG and MRI.
4. Neuropsychological and psychodiagnostic tests: cognitive and adaptive evaluation (WISC, WPPSI-III, Leiter, Bayley, Raven matrices, VABS), ADOS, CBCL, PSI, SCQ.
5. Genetic tests: FMR1, aCGH.

Not all data were available for each patient, especially medical records and tests scores. In particular, scores of VABS, PSI, SCQ were available for very few patients. ADOS and WISC were the most available tests.

3.2 Methods

Patients were divided into two groups:

- A group with High Functioning Autism (n=22), namely a diagnosis of ASD and a normal cognitive functioning, excluding AS individuals, with an age range at the diagnosis of 1–15, including 20 males and 2 females.
- A group with a diagnosis of Asperger syndrome (n=21), with an age range at the diagnosis of 3–17, including 16 males and 5 females.

The data considered for our study analysis were:

- Among anamnestic data: family history, obstetric data (weeks of gestation, weight and length at birth, complications of childbirth, cesarean section), language and motor development data (first steps, first words, delay of language and motor development), hyper-sensitivity, integration or adapting difficulties at school.
- From observation data: gaze hold, language anomalies (phonetic phonological distortions), echolalia, peculiar prosody, vocal stereotypes, fine and gross motor skills, motor stereotypes, sensory research, frustration tolerance.
- From analysis of comorbidities (both from anamnesis and medical evaluation): number of total comorbidities, ADHD, anxiety and/or depressive disorders, specific learning disorders (SLD: dysorthography, dysgraphia, dyscalculia), and other comorbidities.
- From scoring of tests: ADOS, WISC, CBCL by mothers and fathers.
  Among the scores of ADOS tests, the classification and the level of symptoms were considered, because the other sub-scores can differ from one module of ADOS to another.

3.3 Data analysis

The data analysis was made with statistical software *Jamovi.*[1] A first exploration of the data was based on the descriptive statistics of the variables collected.

For the comparison of the qualitative variables, contingency tables were constructed with the absolute and percentage frequencies for each group. To verify if there was a statistically significant difference between the groups, the X^2 (chi-Square) test was performed and significant values with $p < 0.05$ were considered. In cases where there were cells = 0 or more than 20% of cells with value <5 it was not possible from a theoretical point of view to perform chi-square. In these cases, descriptive data were considered. The limit in the execution of the Chi Quadro is linked to the small number of many subgroups.

For the comparison of the quantitative continuous variables, Mann–Whitney U test (nonparametric test of the null hypothesis) was used and values with $p < 0.05$ were considered significant.

[1] The jamovi project (2021). *jamovi*. (Version 2.2) [Computer Software]. Retrieved from https://www.jamovi.org.

4. RESULTS

Through the analysis performed on the population divided in the two groups High Functioning ASD (HF) and Asperger syndrome (AS), statistically significant differences ($p<0.05$) were found in the distribution of:

1. From anamnestic variables: mean age at diagnosis both expressed in years and months (*Table I*).
2. From observation variables: frustration tolerance (*Table XV*); phonetic phonological distortions (*Table XVIII*); echolalia (*Table XIX*); peculiar prosody (*Table XX*); over precise pedantic speech (*Table XXI*).
3. From the analysis of comorbidities: depressive and/or anxiety disorders (*Table XXIII*).
4. From scoring of tests: some subtests of CBCL (*Tables XXVII*).

No differences were found in the distribution of:

1. From anamnestic variables: number of patients with positive family history for psychiatric, neurodevelopment, or neurological conditions (*Table II*); obstetric data (*table III*); delay in motor development (*Table IV*); delay in language development (*Table V*); age at first words and steps (*Table VI*), nutrition (*Table VII*); sleep-wake rhythm (*Table VII*); hypersensitivity (*Table* IX); integration or adaptation difficulties at school (*Tabel X); hetero and auto-aggressive behavior (Table XI and XII*).
2. From observation variables: reduced or absent gaze hold (*Table XIII*), sensorial research (*Table XIV*); gross and fine motor anomalies (*Tables XVI and XVII*); vocal and motor stereotypes.
3. From the analysis of comorbidities: ADHD (*Table XXII*), SLD (*Table XIV*).
4. From scoring of tests: ADOS (*Table XXV*), WISC (*Table XXVI)*, most subtests of CBCL (*Tables XXVII*).

Some of these results need to be interpreted from a descriptive point of view, by the presence of cells = 0 or more than 20% of cells with value <5.

4.1 Anamnestic variables

Table I. Mean age at diagnosis

Age at diagnosis	Group	Mean (±SD)	p
In years	HF	7.14 (±3.92)	0.034
	AS	10.10 (±4.35)	
In months	HF	93.82 (±47.06)	0.032
	AS	129.14 (±48.86)	

Table II. Contingency table: Family history

		Family history		
Group		**Negative**	**Positive**	**Total**
HF	Observed	9	13	22
	% within row	40.9 %	59.1 %	100.0 %
AS	Observed	6	15	21
	% within row	28.6 %	71.4 %	100.0 %
Total	Observed	15	28	43
	% within row	34.9 %	65.1 %	100.0 %

p=0.097

Table III. Obstetric data: weight at birth and length at birth

	Group	N	Mean (±SD)	p
Gestation weeks	HF	18	38.33 (±3.13)	0.736
	AS	19	38.84 (±2.12)	
Weight at birth (g)	HF	13	3153.846 (±451.692)	1.000
	AS	11	3120.455 (±659.471)	
Lenght at birth (cm)	HF	6	50.500 (±1.378)	0.145
	AS	6	49.500 ((±3.332)	

Other data collected, pertaining to obstetric anamnesis, were pregnancy complications (p=0.384), childbirth complications (p=0.449), and childbirth cesarean section (p=0.662)

Table IV. Contingency table: Delay in motor development.

		Motor delay		
Group		**No**	**Yes**	**Total**
HF	Observed	20	2	22
	% within row	90.9 %	9.1 %	100.0 %
AS	Observed	17	3	20
	% within row	85.0 %	15.0 %	100.0 %
Total	Observed	37	5	42
	% within row	88.1 %	11.9 %	100.0 %

p=0.555

Table V. Contingency table: Delay in language development.

		Language delay		
Group		**No**	**Yes**	**Total**
HF	Observed	15	7	22
	% within row	68.2 %	31.8 %	100.0 %
AS	Observed	19	2	21
	% within row	90.5 %	9.5 %	100.0 %
Total	Observed	34	9	43
	% within row	79.1 %	20.9 %	100.0 %

p=0.072

Table VI. Mean age (in months) at first words and first steps.

	Group	**N**	**Mean (±SD)**	p
First words (in months)	HF	14	15.50 (±5.62)	0.099
	AS	14	12.43 (±5.20)	
First steps (in months)	HF	19	13.21 (±1.71)	0.396
	AS	15	14.267 (±3.01)	

Table VII. Contingency table: Nutrition (food selectivity).

		Nutrition			
Group		**Normal**	**Selective**	**Abundant**	**Total**
HF	Observed	12	10	0	22
	% within row	54.5 %	45.5 %	0.0 %	100.0 %
AS	Observed	12	8	1	21
	% within row	57.1 %	38.1 %	4.8 %	100.0 %
Total	Observed	24	18	1	43
	% within row	55.8 %	41.9 %	2.3 %	100.0 %

p=0.549

Table VIII. Contingency table: Sleep-wake rhythm

		Sleep-wake rhythm		
Group		**Regualar**	**Irregular**	**Total**
HF	Observed	14	8	22
	% within row	63.6 %	36.4 %	100.0 %
AS	Observed	18	3	21
	% within row	85.7 %	14.3 %	100.0 %
Total	Observed	32	11	43
	% within row	74.4 %	25.6 %	100.0 %

p=0.097

Table IX. Contingency table: Hyper-sensitivity.

		Sensitivity		
Group		**Normal**	**Hyper**	**Total**
HF	Observed	10	12	22
	% within row	45.5 %	54.5 %	100.0 %
AS	Observed	8	12	20
	% within row	40.0 %	60.0 %	100.0 %
Total	Observed	18	24	42
	% within row	42.9 %	57.1 %	100.0 %

p=0.721

Table X. Contingency table. Integration difficulties.

		Integration difficulties		
Group		**No**	**Yes**	**Total**
HF	Observed	8	14	22
	% within row	36.4 %	63.6 %	100.0 %
AS	Observed	8	13	21
	% within row	38.1 %	61.9 %	100.0 %
Total	Observed	16	27	43
	% within row	37.2 %	62.8 %	100.0 %

p=0.907

Table XI. Contingency Table. Hetero-aggressive behavior.

		Hetero-aggressiveness		
Group		**No**	**Yes**	**Total**
HF	Observed	11	11	22
	% within row	50.0 %	50.0 %	100.0 %
AS	Observed	14	7	21
	% within row	66.7 %	33.3 %	100.0 %
Total	Observed	25	18	43
	% within row	58.1 %	41.9 %	100.0 %

p=0.268

Table XII. Contingency Table. Auto-aggressive behavior.

		Auto-aggressiveness		
Group		**No**	**Yes**	**Total**
HF	Observed	19	3	22
	% within row	86.4 %	13.6 %	100.0 %
AS	Observed	17	4	21
	% within row	81.0 %	19.0 %	100.0 %
Total	Observed	36	7	43
	% within row	83.7 %	16.3 %	100.0 %

p=0.631

4.2 Observation variables

Table XIII. Contingency table: Gaze hold

		Gaze hold			
Group		**Normal**	**Reduced**	**Absent**	**Total**
HF	Observed	6	13	3	22
	% within row	27.3 %	59.1 %	13.6 %	100.0 %
AS	Observed	6	13	1	20
	% within row	30.0 %	65.0 %	5.0 %	100.0 %
Total	Observed	12	26	4	42
	% within row	28.6 %	61.9 %	9.5 %	100.0 %

p=0.635

Table XIV. Contingency table: Sensorial research.

		Sensorial research		
Group		**No**	**Yes**	**Total**
HF	Observed	15	7	22
	% within row	68.2 %	31.8 %	100.0 %
AS	Observed	15	6	21
	% within row	71.4 %	28.6 %	100.0 %
Total	Observed	30	13	43
	% within row	69.8 %	30.2 %	100.0 %

p=0.817

Table XV. Contingency table: Frustration tolerance

		Frustration tolerance		
Group		**No**	**Yes**	**Total**
HF	Observed	13	9	22
	% within row	59.1 %	40.9 %	100.0 %
AS	Observed	5	16	21
	% within row	23.8 %	76.2 %	100.0 %
Total	Observed	18	25	43
	% within row	41.9 %	58.1 %	100.0 %

p=0.072

Table XVI. Contingency table: Gross motricity.

		Gross motor skills		
Group		**Normal**	**Anomalies**	**Total**
HF	Observed	15	7	22
	% within row	68.2 %	31.8 %	100.0 %
AS	Observed	19	2	21
	% within row	90.5 %	9.5 %	100.0 %
Total	Observed	34	9	43
	% within row	79.1 %	20.9 %	100.0 %

p=0.072

Table XVII. Contingency table: Fine motricity

		Fine motor skills		
Group		**Normal**	**Anomalies**	**Total**
HF	Observed	14	8	22
	% within row	63.6 %	36.4 %	100.0 %
AS	Observed	14	7	21
	% within row	66.7 %	33.3 %	100.0 %
Total	Observed	28	15	43
	% within row	65.1 %	34.9 %	100.0 %

p=0.835

Motor stereotypes were also analyzed, they were present in 45.4% of HF patients and 51.2% of AS patients (p=0.317).

4.2.1 Communication

Table XVIII. Contingency table: phonetic phonological distortions.

		Phonetic distortions		
Group		**No**	**Yes**	**Total**
HF	Observed	13	9	22
	% within row	59.1 %	40.9 %	100.0 %
AS	Observed	19	2	21
	% within row	90.5 %	9.5 %	100.0 %
Total	Observed	32	11	43
	% within row	74.4 %	25.6 %	100.0 %

p=0.018

Table XIX. Contingency table: Echolalias

		Echolalia		
Group		**No**	**Yes**	**Total**
HF	Observed	13	9	22
	% within row	59.1 %	40.9 %	100.0 %
AS	Observed	20	1	21
	% within row	95.2 %	4.8 %	100.0 %
Total	Observed	33	10	43
	% within row	76.7 %	23.3 %	100.0 %

p=0.005

Table XX. Contingency table: Peculiar prosody.

		Peculiar prosody		
Group		**No**	**Yes**	**Total**
HF	Observed	11	11	22
	% within row	50.0 %	50.0 %	100.0 %
AS	Observed	4	17	21
	% within row	19.0 %	81.0 %	100.0 %
Total	Observed	15	28	43
	% within row	34.9 %	65.1 %	100.0 %

p=0.033

Table XXI. Contingency table: Over precise, pedantic speech.

		Pedantic speech		
Group		**No**	**Yes**	**Total**
HF	Observed	22	0	22
	% within row	100.0 %	0.0 %	100.0 %
AS	Observed	11	10	21
	% within row	52.4 %	47.6 %	100.0 %
Total	Observed	33	10	43
	% within row	76.7 %	23.3 %	100.0 %

P<0.001

Vocal stereotypes were also analyzed: they were present in 40.9% of HF patients and 19.0% of AS patients (p=0.119).

4.3 Comorbidities

Table XXII. Contingency table: ADHD.

		ADHD		
Group		**No**	**Yes**	**Total**
HF	Observed	12	10	22
	% within row	54.5 %	45.5 %	100.0 %
AS	Observed	17	4	21
	% within row	81.0 %	19.0 %	100.0 %
Total	Observed	29	14	43
	% within row	67.4 %	32.6 %	100.0 %

p=0.065

Attention deficits were also found in other two patients: 1 HF and 1 AS.

Table XXIII. Contingency table: Depressive/anxiety disorders.

		Anxious-depressed		
Group		**No**	**Yes**	**Total**
HF	Observed	20	2	22
	% within row	90.9 %	9.1%	100.0 %
AS	Observed	11	10	21
	% within row	52.4 %	47.6 %	100.0 %
Total	Observed	31	12	43
	% within row	72.1%	27.9%	100.0 %

p=0.005

Table XXIV. Contingency table: Specific learning disorders (SLD).

		SLD		
Group		**No**	**Yes**	**Total**
HF	Observed	19	3	22
	% within row	86.4 %	13.6 %	100.0 %
AS	Observed	17	4	21
	% within row	81.0 %	19.0 %	100.0 %
Total	Observed	36	7	43
	% within row	83.7 %	16.3 %	100.0 %

p=0.631

4.4 Tests

Table XXV. ADOS score:
0= non pathologic, 1=autism spectrum, 2=autistic disorder.

		Classification			
Group		**0**	**1**	**2**	**Total**
HF	Observed	3	6	7	16
	% within row	18.8 %	37.5 %	43.8 %	100.0 %
AS	Observed	1	4	9	14
	% within row	7.1 %	28.6 %	64.3 %	100.0 %
Total	Observed	4	10	16	30
	% within row	13.3 %	33.3 %	53.3 %	100.0 %

P=0.467

Levels of symptoms (high, moderate or low) resulted from ADOS scores were also examined (HF n=11 and AS n=6, p=0.127).

Table XXVI. WISC scores

WISC	Group	N	Mean (±SD)	p
Total IQ	HF	13	102.15 (±12.56)	0.103
	AS	8	109.75 (±14.46)	
VCI	HF	13	106.76 (±12.45)	0.190
	AS	9	115.333 (±14.46)	
RPI	HF	12	111.83 (±18.37)	0.887
	AS	9	113.00 (±22.67)	
WMI	HF	12	82.00 (±12.62)	0.330
	AS	8	88.50 (±13.31)	
PSI	HF	12	96.75 (±9.09)	0.876
	AS	8	100.00 (±16.59)	
GAI	HF	12	110.33 (±14.87)	0.847
	AS	8	113.25 (±19.32)	

Table XXVII. Scores from CBCL compiled by mothers of the patients

CBCL by mothers	Group	N	Mean	(±SD)	p
Internaling	HF	13	67.8	(±8.98)	0.942
	AS	8	67.9	(±7.04)	
Externalizing	HF	13	61.4	(±9.74)	0.088
	AS	8	54.9	(±3.56)	
Total problems	HF	13	65.8	(±9.81)	0.490
	AS	8	64.3	(±5.85)	
Anxious-depressed	HF	13	64.8	(±10.35)	0.771
	AS	8	65.8	(±7.27)	
Somatic complaints	HF	12	61.1	(±7.28)	0.877
	AS	8	61.8	(±7.34)	
Withdrawn	HF	13	70.0	(±13.72)	0.968
	AS	7	69.4	(±12.07)	
Social problems	HF	7	63.7	(±7.70)	0.523
	AS	8	66.8	(±9.63)	
Thought problems	HF	8	63.9	(±9.75)	0.598
	AS	8	65.8	(±10.47)	
Attention problems	HF	13	64.8	(±9.23)	0.102
	AS	8	58.6	(±6.12)	
Rule-breaking behavior	HF	8	57.1	(±7.68)	0.916
	AS	8	55.1	(±3.98)	
Delinquent behavior	HF	13	62.8	(±8.61)	**0.064**
	AS	8	55.1	(±3.91)	
Affective problems	HF	10	65.7	(±13.33)	0.859
	AS	8	66.1	(±10.08)	
Anxiety problems	HF	13	67.2	(±9.64)	0.662
	AS	8	69.1	(±4.45)	
Somatic problems	HF	7	59.1	(±8.76)	1.000
	AS	8	60.3	(7.57)	
ADHD	HF	13	61.4	(±8.56)	0.127
	AS	8	55.3	(±3.15)	
Oppositional defiant disorder	HF	13	62.1	(±7.68)	**0.019**
	AS	8	54.5	(±3.12)	
Conduct problems	HF	8	58.4	(±8.83)	0.526
	AS	8	53.9	(±3.31)	

5. DISCUSSION

5.1 Age at diagnosis

The first aspect that stands out among the results is the difference between the two groups in the patients' age at the diagnosis of their condition. Asperger's children were generally diagnosed later (average age at diagnosis: 10.10 years) than High Functioning ASD ones (average age at diagnosis: 7.14 years), with a p value (p=0.034) obtained by Mann-Whitney function that can state the statistical significance of this age difference. The difference is significant even if considering the age at diagnosis in months (p=0.032). (*Table I*)

The delay in the diagnosis of Asperger syndrome can be attributed to the mildness of its symptoms. In recent years, as Asperger syndrome represents a different functioning, more and more people claim that it is not a true pathological pattern, but only a natural human variation. (67) Furthermore, because it is a chronic condition, often neither patients nor their families realize the existence of clinical symptoms. Signs can become more conspicuous only at times of stress and change, which usually happen during the teenage years. Children may have coped well during their pre-adolescent years, but changes in the nature of friendship, body shape, and school routines may precipitate a crisis that alerts the caregivers and make it possible to discover the condition. Adolescence is also a time of diminishing of the influence of the parents and of increase of the power of identification with the peer group, which can bring out social inclusion problems, and consequently anger and depression. (7)

It is necessary to underline that in high functioning autistic patients, a symptom that can make parents notice the condition earlier is speech delay.

5.2 Familiar, obstetric and physiological anamnesis

No significant differences in family, obstetric and physiological anamnesis between subjects with AS and subjects with HF ASD were observed.

Regarding family history, more than sixty-five percent of the patients in the study (65.1%) had a positive family history of neurodevelopmental, psychiatric, neurological, or genetic disorders. In our sample, familiarity was found mainly for anxiety, mood disorders, autism spectrum disorder, language disorders, and neurological disorders (such as Parkinson's disease, Alzheimer's disease, and epilepsy). A study by M. Ghaziuddin reported a higher rate of familiarity with depression and schizophrenia in AS individuals. (68) In our sample, the number of patients was too little to examine the presence of statistical differences between the two groups for what concerns the familiarity of a specific disease. However, from a descriptive point of view we can say that familiarity with schizophrenia (n=2, 9.5%) was found only in AS group. Moreover, it is interesting to notice that familiarity with language disorders was found only in the HF group (n=4, 18%), whereas in AS patients, who have no language delay or impairment, such familiarity was not found.

Regarding physiological anamnesis, both subgroups presented high frequency of food selectivity (*Table VII.* 41.9% of the total), in accordance with literature (69).

5.3 Language and communication

In our sample, 9 patients presented a history of delay in language development: 7 with High Functioning Autism and 2 with Asperger syndrome. Even if there is an higher percentage of language delay in the HF group (31.8%) versus the AS one (9.5%) with a p value of 0.072, it is important to notice that the presence of lagging language development in Asperger individuals should not even exist according to DSM-IV criteria. Effectively, in DSM-IV the "absence of clinically significant general delay in language" was decisive for AS diagnosis.

The language delay of one AS patient in our study (*patient n. 34*) can be explained by the finding of a congenital hearing loss, with a complete language recovery after the otolaryngology surgery. The language delay of the other AS patient (*patient n. 15*), instead, cannot apparently be explained by other conditions. It is likely that in this specific case, the delay was not considered significant because it was a mild delay (first words at 24 months) with subsequent regular language development. The other clinical symptoms and characteristics of *patient n. 15* were really evocative of Asperger's syndrome.

In any case, various studies have cast considerable doubt over the use of early language delay as a differential criterion between HFA and AS children (Eisenmajer et al. 1998; Howlin 2003; Manjiviona and Prior 1999; Mayes and Calhoun 2001). Tony Attwood, a maximum expert on Asperger syndrome, and many other clinicians, stated that early language delay should not be an exclusion criterion for AS. Attwood underlined that the focus during the diagnostic assessment ought to be on the pragmatic aspects of current language use rather than the history of language development. (7) (70) As a matter of fact, considering language skills instead of language history in our sample, we can find statistically significant differences between the AS group and the HF one. In particular, AS patients showed frequently an over precise, often adult-like, pedantic speech (*Table XXI*. 47.6%), but no phonetic-phonological anomalies (*Table XVIII*. only in 2 cases) or echolalia (*Table XIX*. only in 1 case). HF ASD children, instead, presented frequently phonetic-phonological distortions (*Table XVIII*. 40.9%, p=0.018) and echolalia (*Table XIX*. 40.9% p=0.005), but no pedantic speech. Vocal stereotypes were common in both HF and AS patients, but they tended to be more frequent in HF group. Peculiar prosody was a common characteristic of both subgroups, but it was statistically higher in AS patients (*Table XX*. p=0.033).

5.4 Motor functions

Motor clumsiness has been originally considered a distinctive feature of Asperger syndrome and it was one of Gillberg's criteria (11). In our experience, motor anomalies appeared to be present in both AS and HF groups, without significant difference. These findings agree with more recent studies: Fournier et al. 2010 (71); Nayate et al. 2012 (72).

In particular, for what concern motricity, there were no differences between the two groups in:

- Age at first steps (*Table VI*): mean of 13.21 months for HF, mean of 14.27 for AS (p=0.396).
- Delay of motor development (*Table IV*): 11.9% of the patients, 9.1% of HF and 15.0% of AS (p=0.555).
- Anomaly in gross motricity (*Table XVI*): 20.9% of the patients: 31,8% of HF and 9.5% of AS (p=0.072), with a tendency to significancy towards the HF.
- Anomalies in fine motricity (*Table XVII*): 34.9% of the patients, 36.4% of HF and 33.3% of AS (p=0.835).
- Motor stereotypes: 41.9% of the patients, 31.8% of HF and 52.4% of HF (p=0.317).

5.5 Sensory system

Sensory abnormalities were frequent in our sample, but no significant difference between subjects with AS and subjects with HF ASD was observed. This result agrees with de Giambattista, Concetta et al. study. (37) In particular, the sensory aspects examined in the patients of our study included hypersensitivity (*Table IX*. 57.1% of the patients presented hypersensitivity, p=0.721), investigated through an accurate anamnesis, and sensory research (*Table XIV*. 30.2% of the patients presented sensory research, p=817), evaluated during the visit.

Sensory overload can be experienced by ASD patients as painful and correlated with lower participation in leisure activities and lower performance at school. (37)

5.6 Frustration tolerance and aggressiveness

In our sample low frustration tolerance during the examinations was noticed in a high percentage of patients (58.1%). In a 2012 study by Samson, Huber, and Gross, it was determined that people in the higher functioning part of autism spectrum have higher feelings of nervousness and emotional upset than control individuals who are not on the spectrum. (73) A lot of these feelings are brought on by social difficulties and lack of theory of mind; communication struggles; new unpredictable situations, changing activities or settings; school, work or family expectations; sensory overload.

In AS children the poor frustration tolerance was significantly higher than in HF ones (*Table XV*. p=0.019). This result may be linked to the higher presence of anxiety disorder in this subgroup (*see section 5.7*).

However, the lower tolerance to frustration was not matched by a higher aggressiveness of AS patients compared to HF ones. On the contrary, hetero-aggressiveness was higher in HF patients (HF: 50.0%, AS: 33.3%), even if there wasn't an evident statistical difference (*Table XI.* p=0.631). This may indicate the better compensation capacity of AS rather than HF ASD.

Both subgroups presented high frequencies of auto-aggressiveness as self-injuries and suicide attempts (*Table XII* 16.3% of the total, p=0.268) and hetero-aggressiveness, especially with peers (*Table XI*. 41.9% of the total p=0.631), reported in anamnesis by caregivers.

The presence of relevant difficulties in integration or adapting at school were found in both subgroup with no differences (*Table X.* p=0.907).

5.7 Comorbidities

More than eighty-five percent (86.04%) of the patients in our sample had at least one psychiatric or neurodevelopmental comorbidity. Moreover, 5 patients suffered from epilepsy (11.62%).

Table XXVIII. Comorbidities scheme

Comorbidities	Total		Group				p
			HF		AS		
	N	%	N	%	N	%	
ADHD	14	32.55%	10	45.5%	4	19.0%	0.065
Depressive and/or anxiety disorders	12	27.91%	2	9.1%	10	47.6%	0.005
Specific Learning disorders	7	16.27%	3	13.0%	4	19.0%	0.631
Epilepsy	5	11.63%	2	9.09%	3	14.29%	
Obsessive compulsive disorder	4	9.30%	1	4.54%	3	14.29%	
Developmental coordination disorder	3	6.97%	1	4.54%	2	9.52%	
Psychosis (psychotic episodes)	3	6.97%	2	9.09%	1	4.76%	
Tic disorder	2	4.65%	1	4.54%	1	4.76%	

The most frequent comorbidity in our sample was ADHD (32.55%).

At the age of DSM-IV, it was not possible to perform the diagnosis of ADHD in the context of an ASD, but as research practice and theoretical models suggested that comorbidity between these disorders is relevant and frequent, with a probable genetic overlap, the DSM-5 enabled this co-diagnosis. (44)

Comparing AS and HFA, the ADHD prevalence did not statistically differ between the two groups, showing only a tendency towards HF group (Table 22. p=0.065). The presence of ADHD in both subgroups, with no significant difference between the two, agrees with previous research such as the study of de Giambattista, Concetta et al. (37)

The second more frequent comorbidities were depressive and/or anxiety disorders. These co-occurent diseases were significantly higher in the AS group than in the HF group (*Table XXIII*). p=0.005). In particular, among depressive and anxiety disorders: 7 patients had an anxiety disorder (4 AS and 2 HFA), 1 (AS) patient had a depressive disorder, and 5 (all AS) patients presented a mixed

disorder with both anxiety and depression. This finding agrees with previous literature and studies. (37) (44) The higher frequency of anxiety and depressive disorders may be explained with AS typically higher cognitive and communicative levels, that make them more able in introspection, more conscious of their own social difficulties and so more vulnerable to affective disorders. (37) A bias in this result could be ascribed to the younger age of HF autistics.

None of the other comorbidities showed a statistically significant difference between the two groups. In particular, specific learning disabilities were present in both AS and HF patients (Table 24. p=0.488). This result contrasts with de Giambattista, Concetta at al. study (33) that reported the greater presence of SLD in high-functioning autistic individuals compared to Asperger ones.

Other comorbidities present in few patients of our study were obsessive compulsive disorders (OCD), developmental motor coordination disorder (DCD), psychotic episodes and tic disorders.

5.8 Tests

5.8.1 ADOS

Results of ADOS test were available for 30 patients of the sample (Table *XXV*. HF: n=16 and AS: n=14). Among these patients, 4 had a “non-pathologic” score, 10 were classified as part of the autistic spectrum, and 16 were classified as autistic.
No statistical differences (p=0.467) were found between the two groups.
For both AS and HF ASD patients we can notice the presence of false negative results, which is due to the lower sensitivity of ADOS in the higher IQ patients of the spectrum (48).
The typically higher IQ of AS children versus HF ones, could make think that the sensitivity of the ADOS test could be even lower for this subgroup, but no such difference was found in this sample. Besides, many patients with Asperger

syndrome were diagnosed as proper autistic (*score=1*) and not only part of the spectrum (*score=2*).

No differences were found in the levels (high, moderate or low) of symptoms either (p=0.127).

5.8.2 WISC

Results of WISC test were available for 22 patients, but not all of these patients had the score of all subscales. No significant differences were found in any subscale between the two groups (*Table XXVI*). These data are in contrast with previous literature, which report the higher IQ of AS patients in comparison to HF ones. (33) (37) However, even if our results did not reach statistical differences, we can notice that the average IQ in every scale is higher in AS children than in the HF ones. The scales in which this difference is more relevant are Total IQ (p=0.103) and Verbal Comprehension Index or VCI (p=0.190). The lack of significance could be ascribed to the low number of WISC tests or to a misdiagnosis in HF group of a patient with very high IQ, which heightens the mean IQ of this HF WISC.

Another typical aspect of Asperger syndrome reported in literature is their distinct cognitive profile, characterized by a higher verbal IQ and a lower performance IQ, whereas in most cases of HFA, the pattern is reversed (35) (37). This profile has been linked to the better verbal abilities of AS patients. Other studies did not confirm the existence of this IQ profile, reporting mixed cognitive patterns (74). Our study, from a descriptive point of view, found no difference in the distinguish of VIQ-VIP profile between the two groups, and agrees with studies that reported mixed patterns and no qualitative differences in AS/HFA cognitive profiles. Thus, tests results do not align with clinical evaluation, in which higher language abilities of AS patients are more evident.

5.8.3 CBCL

Twenty-one patients had available results of CBCL test administered to the mothers (n=21) and thirteen patients of CBCL administered to the fathers (n=13). Scores from fathers' tests were very few to be analyzed, thus we considered only mothers' ones. Not all the 21 patients had available scores for all subscales.

In mothers' tests (*Table XXVII*), a statistical difference was found in the distribution of "Oppositional defiant disorder", which was higher in HF patients. A tendency to significancy was also found in "Delinquent behavior", higher in HF patients. If we consider the cut-offs (*non-pathologic / borderline / pathologic*) of the scores of this subscale rather than continuous score, we can find a statistical difference (p=0.040). This result reflects clinical data of hetero-aggressiveness, which, on the other hand, did not reach significance (*Table XI*). (*See section 5.6*)

No differences were found in anxiety and depressive disorders, differently from clinical results (*see section 5.7*).

5.9 Study limitations

Limitations of the study certainly lie in its retrospective nature, which limits the homogeneity, because of the risk of bias of selection, and completeness of the information collected. The bias of selection can be ascribed to the exclusion from the study of patients that had no report of a cognitive evaluation. In many cases ASD patients had data of development evaluations (Bayley Scales, that provide a developmental quotient rather than an intelligence one) and no data of cognitive evaluation (Wechsler Scales, Leiter Scale, Raven Matrices etc.).

The incompleteness of the information collected is due to the fact that ASD patients who come to the Neuropsychiatric Unit to carry out organic and second-third level investigations often do not carry out a complete diagnostic evaluation, that's why the results of many tests were not available for all patients. It would be important to expand the sample size and design a prospective study.

5.10 Overview table

Table XXIX. Overview table

	AS	HFA
Autistic core features (i.e. deficits in social communication and interaction and restricted, repetitive patterns of behavior, interests, or activities) False negative results in ADOS in both subgroups	Present	Present
Age at diagnosis	Older age at diagnosis	Younger age at diagnosis
Family history: familiarity for anxiety, mood disorders, language and neurological disorders **Obstetric anamnesis** **Physiological anamnesis**: Common selective nutrition	No differences	No differences
History of language development **Communication skills**	Absent or mild language delay More frequent peculiar prosody More common over-precise or pedantic speech (with overly formal speech, similar to an in-depth monologue about a topic of special interest)	Common language delay More phonetical-phonological distortions and echolalia (Vocal stereotypes higher but not significantly)
Anomalies in motor development, gross and fine motricity, motor mannerism	No differences	No differences
Reduced gaze hold	No differences	No differences
Atypical sensitivity	Frequent	Frequent
Integration difficulties at school	Common	Common
Reduced frustration tolerance	Frequently reduced	Sometimes reduced
Hetero-aggressive behavior **Auto-aggressive behavior**	Frequent	Frequent (higher aggressive behavior according to CBCL)
Comorbidities The most frequent was ADHD SLD, OCD present in both	Depressive and anxiety disorders significantly more common in AS than in HFA	
Cognitive profile (WISC): full Scale IQ e subvalues Mixed cognitive profiles	All subscales higher in AS (no statistical difference)	

6. CONCLUSIONS

Although Autism and Asperger's syndrome are currently conceptualized as being part of the same continuum, the results of this study suggested the presence of quantitative but also qualitative differences especially in language and communication, and in comorbidity profile. However, from a merely clinical point of view, similitudes appear greater than differences.

It is expected that future studies will clarify more precisely whether there are significant differences or similarities between the two conditions, to guide a better therapy when necessary and individualized treatments.

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