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CHAPTER 1

1.1 INTRODUCTION TO THE ISSUE

The last several years have seen an increasing amount of new evidence that allowed a greater knowledge and understanding of how cognitive, emotional, behavioural and relational skills emerge and develop throughout the brain maturation, and highlighted some factors which may account for their presentation as mental health conditions or mental health problems.

In the field of Intellectual Disability (ID) the most appropriate framework is provided by the neurodevelopmental perspective, because it permits not only to explain the relations across systems but also to justify the need of researchers and practitioners who work for the development of multi-level and interdisciplinary approaches focused on the aetiological comprehension and interventions of mental health problems.

The neurodevelopmental perspective integrates the principles of core developmental psychology/psychobiology theories and models with those derived by developmental and cognitive neuroscience, and localises positive and pathological adaptations in the transactional relations between the individual's internal biological/psychological mechanisms and the external environment.

It represents a dimensional approach, which viewing illnesses on a continuum with normality is more sensitive to the individual's changes across development. Therefore, it offers many advantages for neuroscience and genomics in respect to the categorical approaches.

One of the most important consequences of such neurodevelopmental perspective is the appreciation that what have been previously considered as distinctive disorder categories actually share some features, and may co-occur or become evident as a sequential comorbidity, or instead represent a different age-adjusted presentation of the underlying brain mechanisms. The hypothesis regarding shared features between disorders has been supported by recent genome-wide association studies, showing that copy number variants of several syndromes as ID are also present in many autism-spectrum disorders, as well in other major psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder. The recent findings revealing a genetic overlap for most of these disorders fostered the suggestion that they may constitute part of a unique group of disorders affecting the neurodevelopment (Owen, 2012).

A developmental approach characterizes also the new Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and it is particularly evident in the new section dedicated to the 'Neurodevelopmental Disorders' (American Psychiatric Association - APA, 2013), which replaced the 'Disorders usually first diagnosed in infancy, childhood, or adolescence' section of DSM-IV-Text Revised (TR) (APA, 2000). In this section the disorders have been organized not taking into account necessarily the childhood or adolescence onset; instead, they have been clustered in a new meta-structure in consideration of the shared symptoms, shared genetic and environmental risk factors, shared neural substrates, common cognitive dysfunctions such as limitation of learning,

deficits in executive functions and impairments in communication and social skills. Moreover, the co-occurrence of these conditions is now accepted.

It is important to emphasize that this new group of conditions poses a challenge for clinicians and researchers, requiring more attention in the differential diagnosis and in the assessment for the presence of comorbidities. This is especially important in relation to ID, Autism Spectrum Disorders (ASD) and Schizophrenia Spectrum Disorders (SSD), in consideration of the co-occurrence of ASD and SSD in individuals with ID (Bertelli et al., 2015).

In the last five years, the prevalence of autism increased greatly. Currently, the prevalence rate for ASD in adults is more than 1/100, whereas it was 0.5/1.000 in the 60s. Obviously, the reasons for such increase have posed some questions.

It is possible that the greater awareness about the condition and the changes in the diagnostic criteria, in particular the introduction of a wide autistic spectrum with the DSM-5, may have played a role. Methodological differences among studies may provide further explanation (Wing and Potter, 2002; Fombonne, 2009; Matson & Kozlowski, 2011).

Some environmental factors have been suggested to be the cause of such ASD increased prevalence, particularly the triple vaccine for measles, mumps and rubella (MMR). However, there is not enough evidence to confirm their etiopathogenetic role (Wing & Potter, 2002; Rutter, 2005); conversely, a stronger evidence supports the role of complex genetic factors in the emergence of the disorder. Findings by family studies (Tarpey et al., 2009; Shoubridge et al., 2010; Noor et al., 2010) showed the existence of early markers, and helped to define a broader autism phenotype in respect to the conceptualization suggested by Kanner (Kanner, 1973; Ching et al., 2010; Fisch et al., 2011; Georgiades et al., 2011).

Among other factors considered to play a role in the increasing number of ASD diagnoses are the growing awareness and knowledge among the public, parents and professional workers, as well the development of specialist services (Wing & Potter, 2002; Fombonne, 2009; Matson & Kozlowski, 2011). Since the 1960s, a growing interest in autism led to the development of parent voluntary associations, which demanded educational and treatment services for their offspring and fostered research in the area. The intensification of scientific interest in autism is evident in the higher number of published epidemiological studies on autism, there were only 23 in 1999, rising to 32 in 2003 (Fombonne, 2003) and to 53 in 2009 (Fombonne, 2009).

It is worth noting that in most of the countries where it was documented an increased prevalence of ASD it was also noticed a decrease in the number of ID diagnoses (Newschaffer et al., 2007; Baron-Cohen et al., 2009; Lazoff, 2010). This finding presents some epidemiological, social and economic implications. Evidence shows that since the late 1970s, the number of specialized and educational institutes for people with Mental Retardation (MR) was gradually reduced whereas that of those addressed to the care of children and adults with autistic disorders has increased (Wing, 2001). It has been suggested that the greater availability of services can have determined a tendency among

professionals to make a diagnosis of autism, rather than another condition, because it allowed receiving more adequate support (Matson & Kozlowski, 2011).

The great variability in ASD prevalence rates across studies has been also associated with the different methodologies for collecting data, such as the use of registries, hospital records, reports from community outpatient clinics and also retrospective reporting. The differences in such case finding and population sampling inevitably affect the prevalence estimates. Not to mention that information about age group and the rates of non-response are key elements for interpreting the prevalence rates of ASD (Posserud et al., 2010; Sun et al., 2013).

Finally, the variance in prevalence estimates may be also a consequence of different assessment methods and diagnostic instruments used (Groen et al., 2007; Oosterling et al., 2009; Posserud et al., 2010; Lord, 2011).

The diagnosis of ASD is challenged by the high rate of comorbidity with ID/IDD (Intellectual Developmental Disorder) and SSD, requiring a more accurate assessment in order to disentangle the contribution of each disorder to the clinical presentation and the associated mental distress (Bradley & Bolton, 2006; Palucka et al., 2008; Bradley et al., 2011a,b).

1.2 AUTISM AND AUTISM SPECTRUM DISORDER

1.2.1 DEFINITION AND DIAGNOSTIC CRITERIA: EVOLUTION AND CURRENT STATE

There are three key features that characterize autism. These are: impaired ability to socialize, (e.g. reluctance to make eye-contact, lack of appropriate peer relationships, lack of emotional reciprocity), poor communication skills (e.g. delay in verbal responses, poor conversation skills, lack of pretend play), and restricted and repetitive behaviours or interests (e.g. repetitive motor movements, preoccupation with parts of objects) (Briegel et al., 2009; Matson et al., 2009a,b; Gillberg, 2010; Horovitz & Matson, 2010; Leung et al., 2010; Smith & Matson, 2010a,b,c).

The term autism was coined by Eugen Bleuler to describe a kind of schizophrenia mainly characterised by individuals 'inward turning' into his/her own world and thereby losing contact with the outer world. Bleuler's overall conceptualisation of schizophrenia is focused on the loss of interpretative and relational skills, as summarised in the 4A theory: inappropriate or flattened Affect, Ambivalence towards others, loosening of thought Associations, and Autism, which was defined as 'social withdrawal' and 'preference for living in a fantasy world' rather than interacting appropriately with the social world (Bleuler, 1911; 1950).

In 1944, Asperger used a similar term 'Autistischen Psychopathen', to describe some patients who were surprisingly similar to those described by Kanner. Asperger noted three significant differences: 1) more fluent speech; 2) difficulty in carrying out large movements but not fine movements; 3) a different level of learning ability. He called his patients 'abstract thinkers', which, according to Kanner, have great problems with mechanical learning. Even with important common traits, two different clinical forms were determined - Kanner's autism and Asperger's syndrome. Subsequently, Asperger's syndrome became the term applied to the autistic people with a relatively high IQ (Intelligent Quotient; high-functioning autism).

Lorna Wing, a British psychiatrist born in 1928, the mother of an autistic child and the founder of the National Autistic Society in the UK, distinguished three types of social interaction:

- CONFIDENTIAL: individuals indifferent to other people, detached, characterized by the presence of motor stereotypes, good mechanical skills and visual-spatial abilities, and medium-severe cognitive impairments (autistic disorder).
- PASSIVE: autistic disorder with fewer symptoms that are detected later in life.
- STRANGE: people who are a bit 'naïve', but with good cognitive abilities (high-functioning autism).

During the 1950s and 1960s, autism was considered an early manifestation of schizophrenia, which was thought of as an emotional disorder caused by pathological parent-child interaction.

In the first two editions of the DSM, autism was classified under the terms 'schizophrenic reaction, childhood type' (APA, 1952) and 'childhood schizophrenia' (APA, 1968), respectively.

During the 1970s, the psychogenic paradigm was abandoned and the scientific community started thinking that autism is a biological disorder, and is not caused by cold parents. Autism was also no longer considered incompatible with MR. Even in the 1960s children showing several signs of autism, co-occurring MR, and childhood psychosis were described.

In the 1960s and 1980s there was still a clear controversy over the definition of autism between the international nosographic systems. The International Classification of Diseases - Ninth Revision, ICD-9 (WHO, 1980) considered autism a diagnostic subcategory of the childhood schizophrenia. The DSM-III (APA, 1980) introduced 6 diagnostic criteria for infantile autism including early onset within 30 months of age, communication and language disorders, narrow interests and fear of change. For the first time the distinction between schizophrenia and autism was emphasized and the definition of Pervasive Developmental Disorder (PDD) was introduced. Five disorders comprised this diagnostic category and included infantile autism, residual infantile autism, childhood onset pervasive developmental disorder, residual childhood onset pervasive developmental disorder, and atypical autism. Bringing forward the concept of 'syndrome', possible symptoms including the bizarre movements, problems of affectivity, abnormal speech, hyper- or hyposensitivity, self-harming behaviours, anti-social behaviours, and lack of empathy were mentioned.

The DSM-III-R (APA, 1987) provided a more complex definition and the diagnosis required that an individual had to exhibit at least 8 of these 16 criteria in the three areas of social interaction, communication/imagination and interest/activity. The age of onset was revised and shifted to 'within the first 36 months of life'. A new diagnostic category under the term of PDD-Not Otherwise Specified (PDD-NOS) was introduced. PDD-NOS was defined by subthreshold symptoms, too mild to allow a diagnosis of real autism that should be considered if a child does not meet the diagnostic criteria for a specific PDD. Revisions made in the DSM-III-R included changing infantile autism to autistic disorder, while childhood onset pervasive developmental disorder and residual infantile autism were dropped.

The DSM-IV (APA, 1994) further refined the diagnostic criteria and increased the number of PDD to five: autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and PDD-NOS. The DSM-IV adds autism to the general chapter 'global alterations of psychological development' and particularly to 'generalized developmental disorders'.

In the DSM-IV-TR (2000) the diagnostic categories and criteria remained consistent from the earlier edition.

According to the revision of the IV edition of DSM (DSM IV-TR) valid until May 2013, the diagnosis of autism requires the following criteria:

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

(1) qualitative impairment in social interaction, as manifested by at least two of the following:

a) marked impairments in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
b) failure to develop peer relationships appropriate to developmental level

c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest)
d) lack of social or emotional reciprocity

(2) qualitative impairments in communication as manifested by at least one of the following:

a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
c. stereotyped and repetitive use of language or idiosyncratic language
d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(3) restricted repetitive and stereotyped patterns of behaviour, interests and activities, as manifested by at least two of the following:

a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
b. apparently inflexible adherence to specific, non-functional routines or rituals
c. stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
d. persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

(1) social interaction

(2) language as used in social communication

(3) symbolic or imaginative play

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Given the extreme variability in autistic symptoms, which has been widely described by clinicians and researchers during the past 15 years, the authors of the DSM-5 substantially revised the concept of autism and PDD. The DSM-5 combined four previously separate disorders into a single condition under the heading of ASD with different levels of symptom severity. The previous DSM-IV autistic disorder, Asperger's disorder, childhood disintegrative disorder, and PDD-NOS (atypical autism) are not recognized anymore as single nosological entities, while the Rett's disorder became an independent disorder, with a specific genetic etiopathogenesis. The diagnosis of ASD requires two core symptoms: a) deficits in social communication and social interaction and b) restricted repetitive behaviours, interests, and activities (Achkova & Manolova, 2014).

The chronological criterion for the onset of symptoms has been widely modified from 36 months to 'early childhood', with the possibility of other ages of onset in the situations in which deficits may not become fully manifest until social communication demands exceed limited capacities.

Some researchers have criticized the DSM-IV-TR and DSM-5 approach, considering responsible for both the widening of diagnostic criteria and the progressive increase in prevalence rates of autism spectrum conditions (Wing et al., 2011).

According to DSM-5 the ASD diagnostic criteria include:

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understand relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history:

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals).
3. Highly restricted, fixated interests that are abnormal in intensity or focus
4. Hyper- or hyporeactivity 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).

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).

The DSM-5 defines three levels of severity based on the adaptive functioning:

- Level 1: Requiring support
- Level 2: Requiring substantial support
- Level 3: Requiring very substantial support

The disorder has been placed in a meta-syndromic or meta-structural grouping named ‘Neurodevelopmental Disorders’ which includes:

- Autism Spectrum Disorder
- Intellectual Disability (Intellectual Developmental Disorder)
- Communication disorders
- Attention-Deficit/Hyperactivity Disorder
- Specific Learning Disorder
- Motor Disorders

The neurodevelopmental disorders comprehend conditions with onset in childhood, typically early, often prior to entry to school, and are characterized by developmental deficits which produce impairments of the personal, social, academic, or occupational functioning. The range of

developmental deficits varies from very specific limitations in learning and executive functions to the global impairment of social skills or intelligence. The neurodevelopmental disorders frequently co-occur together; for example people with autism often have ID.

However, the debate on the final drafting of the autism core symptoms is still in vigour. Some authors suggest centring the diagnosis on repetitive behaviour and stereotypes, while others on sensorial sensitivity (Billstedt et al., 2007; Leekam et al., 2007; Happé & Ronald, 2008).

1.2.2 EPIDEMIOLOGY

In the last decade the prevalence of autism has increased considerably. In the 1960s the highest reported rate was 0.5/1.000, whereas it currently stands at 1–2/1.000 (Newschaffer et al., 2007). Also the recorded prevalence of ASD has increased dramatically and they are now considered the most common disorders in childhood, with a rate of 6/1.000 (Newschaffer et al., 2007; Fombonne, 2009). A 2009 American report (Boseley, 2009) based on the 2007 Adult Psychiatric Morbidity Survey by the National Health Service in the UK, estimated that the prevalence of ASD in adults was approximately 1/100 (Brugha et al., 2011). A recent study (2011) conducted by Kim and colleagues at the University of Yale found that about 2.64% of South Korean children are affected by autism.

The age of onset traditionally occurs early in the first years of life (Ozonoff et al., 2008). The male-to-female sex ratio is approximately 3-4/1 (Newschaffer et al., 2007).

1.3.3 ETIOPATHOGENESIS

Definitive etiopathogenetic mechanisms of ASD have not yet been identified. Currently the international scientific community is inclined to consider a complexity of different causal elements including both environmental and biological factors, especially genetic ones. Their combination may induce structural and functional defects of the Central Nervous System (CNS) in the first years of life and may produce the characteristic phenotype of autism. The current theories suggest that autism disorder resulted from the disruption of normal brain development with subsequent effects on cerebral functioning related to the specific symptoms of ASD (Watts, 2008).

Genetic factors

Genetic mutations appear to be a major cause of autism. More than one gene may be implicated and several candidate genes have been located. Submicroscopic chromosomal abnormalities have been identified in almost 1/5 of cases (Shen et al., 2010; Schaaf & Zoghbi, 2011; Silver & Rapin, 2012), whereas ASD-linked mutations of many candidate genes have been identified. The heritability of autism showed that 82-92% of monozygotic and 1-10% of dizygotic twins develop ASD (Persico & Bourgeron, 2006). Furthermore, autistic symptoms are usually observed in many genetic syndromes, such as fragile X, tuberous sclerosis, phenylketonuria and congenital rubella (Freitag, 2006; Betancour et al., 2009).

Among the genes associated with autism risk, many code for proteins involved in regulating proper synaptic connectivity and brain functioning (Folstein & Rosen-Sheidley, 2001; Persico & Bourgeron, 2006).

Recent methodological advances of human genetics increased knowledge on the biological processes of ontogenesis and allowed the discovery of new DNA variants in ASD including the Copy Number Variations (CNVs) (Marshall & Scherer, 2012). CNVs are defined by a polymorphism from spontaneous deletions to duplications involving one or more DNA nucleotide. In the last years many studies found robust association between CNVs and ASD, mediated by specific structural and functional alterations of the CNS (Watts, 2008).

In 2004, to provide a better description of the ASD risk-associated genes, the Autism Genome Project (AGP) was launched. AGP is the world's largest research project on DNA mapping and included analysis of DNA samples from approximately 1.200 families. The AGP discovered the involvement of chromosome 11 in the pathogenesis of autism, along with the gene coding for the Neurexin 1 (NRXN1), a protein involved in synapse formation and synaptic transmission. Also dysfunction of the Neuroligin (NLGN), a cell adhesion protein on the postsynaptic membrane that mediates the formation and maintenance of synapses, was implicated in ASD. Mutations of the NRXN1 and NLGN genes have been also associated with schizophrenia, and ID (Szatmari et al., 2007; Südhof, 2008).

Additionally, one of the most studied genes was SHANK3 (SH3 and multiple ankyrin repeat domains 3) located on chromosome 22 and coding for the protein with the same name, also known as ProSAP2 (Proline-rich synapse-associated protein 2), which is involved in synapses formation and in dendritic spines maturation as well as in the connection of various neurotransmitters receptors, ionic channels and other membrane proteins to the actin cytoskeleton (Durand et al., 2012).

Epigenetic mechanisms

Although increased evidences indicate genetic factors as the main cause of autism, this does not seem to explain all the current etiopathogenetic instances. In fact, epigenetic mechanisms that alter gene expression and phenotype without changing the DNA sequences, seem play a key role in the etiopathogenetic mechanisms of ASD.

DNA methylation is the most widely studied, and also environmental toxins exposures are known to influence epigenetic modifications prenatally and throughout life (LaSalle, 2011; Zhubi et al., 2014; Loke et al., 2015).

Interestingly, Rett syndrome is an X-linked disorder characterized by ID, inability to perform motor functions and autistic-like behaviours. This syndrome seems to be caused by an epigenetic alteration in the gene encoding methyl-CpG binding protein 2 (MECP2), which binds to methylated regions and activates the deacetylation of histones, inducing DNA inactivation. Decreased MECP2 levels have also been found in the cerebral cortex of people with ASD (Woods et al., 2012).

Biological and environmental factors

Environmental factors have been considered to contribute to autism or exacerbate its symptoms. Infections such as congenital rubella syndrome or cytomegalovirus may occur during pregnancy and increase the risk of autism (Libbey et al., 2005). The possible contribution of allergic or mother's immune response during the pregnancy was supported by findings of maternal antibodies reactive to foetal brain proteins, which also seems to indicate their ability to pass through the blood-brain barrier and affect the development of brain.

Toxic substances, which act through their teratogen potential and cause birth defect, include pesticides, phthalates, alcohol and some drugs, such as terbutaline, thalidomide, misoprostol, and valproic acid (Gardener et al., 2009). Toxic metals such as antimony, arsenic, cadmium, chromium, lead, mercury, manganese, nickel, styrene, trichloroethylene, methylene chloride, vinyl chloride and particulate of diesel are associated with ASD. Also the prenatal exposure to high air pollution containing many toxins impact negatively on the neurological function seems doubles the chance of developing ASD (Roberts et al., 2013).

Scientists have spent years debating whether the use of common antidepressants during pregnancy could increase the risk of ASD. Boukhris et al., (2015) has recently published several reports suggesting that suggests that maternal exposure to selective serotonin reuptake inhibitors during pregnancy is associated with an increased risk of autism, but this causal relationship does not seem supported by clear evidence (Croen et al., 2011; Antrade, 2014; El Marroun et al., 2014; Kepser & Homberg, 2014; Jones & McDonald, 2014; O'Dowd, 2014; Suri et al., 2014).

On the contrary, metabolic problems that affect mothers during pregnancy, especially type 2 diabetes, was significantly associated with an increased risk of ASD. Also maternal obesity during pregnancy may also increase the risk of autism, although further study is needed (Krakowiak et al., 2012; Li et al., 2015).

It has been hypothesized that high levels of amniotic testosterone could play a role in ASD. Prenatal testosterone levels seem to play an important role in brain development by influencing communication skills and empathy and emphasizing masculine characteristics (Auyeung et al., 2009; 2010).

Autism is associated with some perinatal and obstetric conditions including low birth weight, abnormal gestation length and hypoxic-ischaemic insult at birth (Kolevzon, 2007).

Furthermore a broad variety of postnatal contributors to autism have been proposed, including: autoimmune diseases (Ashwood & van de Water, 2004), leaky gut syndrome (Johnson, 2006), amygdala developmental failure (Schultz, 2005), vitamin D deficiency (Cannell, 2007), and heavy metal toxicity (Davidson et al. 2004). For the majority of those risk factors, there is no definitive evidence of a causal or co-causal role in the development of ASD.

Some researches indicate that oxidative stress may cause autism in individuals who are genetically predisposed (Kern & Jones, 2006). One theory is that stress increase the secretion of Corticotrophin-Releasing Hormone (CRH) which stimulate mast cells to release cytokines, increasing the blood-brain

barrier permeability and damaging the functional and structural integrity of Purkinje cells in the cerebellum (Chauhan & Chauhan, 2006).

Recently, food substances containing gluten and casein have been implicated in ASD, but their pathogenic mechanism of brain damage has not yet been clarified (Mari-Bauset et al., 2014).

Among these factors, childhood vaccinations, especially the Measles-Mumps-Rubella (MMR) vaccine, and the subsequent development of autism vaccines, have attracted considerable attention. First Andrew Wakefield, a British physician known for his fraudulent 1998 paper, suggested that MMR antibodies were significantly higher in the gut of autistic children, but this association was never backed up by extensive evidence based on a large sample of observations (Wilson et al., 2003; Chen et al., 2004; Afzal et al., 2006; Taylor et al., 2014).

In 2013, Prof. Frank DeStefano and colleagues from the U.S.A. CDC (Centers for Disease Control and Prevention) conducted a study on over 1.000 children with and without autism. This study did not found any link between ASD and the antigens contained in the vaccine, which determine the activation of the immune system.

Also the exposure to heavy metals was also suspected of increasing the risk of ASD. In particular the hypothesis involved the use of the mercury-based compound thiomersal, a childhood vaccinations preservative. There was an enormous debate, but once again, large-scale research showed that children vaccinated with products with and without mercury have the same risk of ASD occurrence. The stronger evidence is that the autism rate has remained unchanged since the 2002 when the thiomersal was completely removed from paediatrics vaccines (Roberts & Harford, 2002; Stratton, 2012).

Neuroanatomical abnormalities and neurotransmitters system

Functional Magnetic Resonance Imaging (fMRI) allows researchers to observe directly brain activities while subjects perform various perceptual, and cognitive tasks. Brain-imaging techniques like fMRI have shown altered functional patterns in several domains of thinking, such as social, cognitive, linguistic, and visuospatial processing in children and adults with ASD (Maximo et al., 2014). Autism appears to result from developmental factors that affect many or all functional brain systems. Today a very plausible hypothesis suggests that disrupted connectivity should be seen as part of the primary pathogenesis of ASD. Evidence showed both of local over-connectivity and of long-distance under-connectivity that appear more severe in later-developing cortical regions (Minshew & Keller, 2010; Muller et al., 2011). The disconnection of the neural circuits could lead to deficits in complex information processing and integration (Mizuno et al., 2006; Turner et al., 2006; Courchesne et al., 2001, 2007; Geschwind & Levitt, 2007; Noonan et al., 2009). Disconnection of the nervous structures would be realized at the level of histogenetic processes passing through the period of brain development which begins in the uterus and extends into childhood that include neurogenesis, neuronal migration, dendritic development, synaptogenesis, synaptic pruning and dendritic plasticity and myelination. Some researches reported an overall brain enlargement, while others suggested

abnormalities in several areas, including the frontal lobe, limbic system, temporal lobe, and corpus callosum (Stanfield et al., 2008; Lefebvre et al., 2015). It is probable that each of these neurodevelopmental processes may be involved in the disconnection mechanisms, which could extend to communications between cortical and subcortical areas and result in a considerable heterogeneity of ASD phenotypes.

Many neuroanatomical studies focused on the cerebral structures and neural circuits crucial for the ASD symptoms:

1) difficulty in social interactions has been related to dysfunctions in the orbitofrontal cortex, anterior cingulate cortex, fusiform gyrus, superior temporal sulcus, amygdala, mirror neurons, inferior frontal gyrus and posterior parietal cortex;

2) deficits in language development and communication skills have been related to the dysfunction of the inferior frontal gyrus - Broca's area, superior temporal sulcus, supplementary motor area, basal ganglia, thalamus, and cerebellum pontine nuclei;

3) repetitive behaviours, ritualized and restricted range of interests have been related to dysfunction of the orbitofrontal cortex, anterior cingulate cortex, basal ganglia, and thalamus.

However, contradictory information was recorded on the total volume content. Studies observed increased (Minshew et al, 2005) or decreased total size, as well as smaller posterior subregions of the corpus callosum (Courchesne et al., 1993; Stanfield et al., 2008; Hardan et al., 2009). Other researches found microstructural abnormalities mainly concerning a reduction of Purkinje cells of the cerebellum (Bauman & Kemper, 2005). The cerebellum in the past was considered to be involved exclusively in motor function, while today it has been associated with broader functions including cognition and emotional regulation.

The amygdala is involved in many significant processes of social cognition. Increased, reduced or normal amygdala volume has been described (Howard et al., 2000; Eigisti & Shapiro, 2003; Schumann et al., 2004; Stanfield et al., 2008).

Despite the importance of communication and language deficits in autistic individuals, there are many studies that examined the neuroanatomical areas that perform these functions. The areas of language include: Broca’s area in the inferior frontal gyrus implicated in expressive language, Wernicke’s area in the temporal-parietal region implicated in receptive language and the superior temporal sulcus which play a role in both the processing of language and social attention. Lesions to the language centre resulted primarily in alterations of the normal pattern of asymmetry (De Fossé et al., 2004; Rojas et al., 2005; Redcay, 2008).

Investigations into other brain regions that may be involved in autism are limited. Abnormalities of the thalamus (Hardan et al., 2006), hippocampus (Schumann et al., 2004; Nicolson et al., 2006; Dager et al., 2007), and basal ganglia (Hardan et al., 2003; Hollander et al., 2005) were found. In particular, studies highlighted that repetitive and ritualistic behaviours were associated with larger increases in caudate volume (Hollander et al., 2005).

Recent evidences provide a better understand of neurotransmitter mechanisms regulating social behaviour. Oxytocin and vasopressin neuropeptides play an important role in social cognition, affecting individual differences in social recognition, and parenting or affiliative behaviours. The processes of social cognition are also supported by reward circuitry, underpinned by the activation of the brain dopaminergic system. Reward processes play a role in the development of social skills, parenting and pairing, and also influence social interactions, which require trust or altruism. The effect of emotional regulation upon social behaviour is also mediated by norepinephrine and serotonin systems (Skuse & Gallagher, 2011).

Electrocortical alterations

Some neurophysiological investigations on individuals with ASD reported abnormal frequency range (30-80 Hz) in neuronal synchronizations related to alterations in sensory and cognitive functioning, especially in working memory and perceptual binding (Saunders et al., 2012).

Networks of GABAergic interneurons are implicated in synchronizing cortical activity, and seem to play a fundamental role in cognitive functions, such as attention and sensory processing (Rubenstein & Merzenich, 2003; Endele et al., 2010).

Imbalance between excitation, inhibition and increased excitatory-inhibitory (E-I) ratio is a common mechanism in ASD, which is responsible for learning and memory as well as cognitive, sensory and motor deficits, and seizures occurring in these disorders. E-I imbalance in ASD is due primarily to abnormal glutamatergic and GABAergic neurotransmission in key brain regions such as the neocortex, hippocampus, amygdala, and cerebellum (Uzunova et al., 2015).

Mirror neurons

It has also been proposed that deficiency of the mirror neuron system may underlie cognitive disorders in individuals with autism. Mirror neurons were first discovered by Giacomo Rizzolatti and his colleagues at the Department of Neuroscience of the University of Parma (Rizzolatti et al., 1996). Using electrodes implanted in the pre-motor cortex of the macaque monkey, the researchers observed that some groups of neurons were activated not only when animals were intent on certain actions, but also when watching someone else perform the same actions. Subsequent studies, carried out with non-invasive techniques, demonstrated the existence of similar system in humans. Various areas in the brain contain mirror neurons such as those of language, and provide a physiological explanation of our ability to position ourselves in relation to others. When we observe another perform an action, our brain activates the same neurons that come into play when we perform that action, or alternatively the same neurons that came into play when we undertook similar actions in the past. In fact, it seems that the mirror system comes into action only when the subject observes a behaviour that he himself has previously performed. Even the recognition of emotions seems related to a group of neural circuits in which the same mirror feature was observed. Experimental studies on primary emotions show that

when one observes others' facial expressions of disgust or pain the same neural substrate connected to the first perception is activated. Furthermore, clinical trials confirm that the loss of ability to feel emotions caused by neurological damages may lead also to lose the ability to recognize and interpret another person's emotions.

The discovery of mirror neurons may provide a biological explanation for at least some forms of autism, such as Asperger's syndrome. In fact, experiments seem to indicate decreased functioning of these neurons in autistic children. Although this is just a hypothesis, it may help to understand why autistic people do not participate in the life of others, can not empathize with the world around them, and do not understand the meaning of the gestures or actions of others (Gallese & Goldman, 1998).

Theory of mind

Uta Frith and Simon Baron-Cohen identified a deficit in the Theory of Mind (ToM) as the base of the difficulties of people with ASD to interact with others and with the outside world. Baron-Cohen described the ToM as the ability to infer a complete range of mental states including beliefs, desires, intentions, imagination, emotions, etc. from observable behaviour. To have a theory of mind means to be able to attribute intentional (desires) or epistemic (beliefs) mental states to oneself and to others, and to predict the behaviour of oneself or others on the basis of individual 'internal' mental states which determine those behaviours (Baron-Cohen, 1991).

The concept of theory of mind is closely related to the more general concept of metacognition. The ToM would be a specific aspect of a broader range of metacognitive skills acquired during ontogenetic development. Metacognition refers to a set of skills which makes it possible to recognize and attribute mental states to others starting with facial expressions, somatic states, behaviours and actions. Metacognition also makes it possible to estimate mental states and to use the resulting information to make decisions, to solve problems, and to master subjective suffering (Semerari et al., 2012).

Deficits in metacognitive capacity were associated with damage to the prefrontal cortex, superior temporal sulcus, front part of the temporal lobes and amygdala.

Some phenomenologists and psychopathologists have recently expressed many doubts that the ToM plays a causal role in ASD, and more generally in the processes of social cognition. Studies have found that many people with ASD and psychotic disorders consciously observe and imitate the behaviours of others. According to these researchers the process of the perception of others would be conscious, finalized, and would not require any theory or simulation. For people with ASD the practice of explicit mind-reading seems to be a compensatory strategy which ultimately fails, and may even exacerbate their deficit of intuitive and interactive social understanding. A lack of embodiment interaction represents a valid alternative (Froese et al., 2013a,b; Gallagher & Varga, 2015).

1.2.4 PROBLEMS ASSOCIATED WITH AUTISM AND AUTISM SPECTRUM DISORDER

ASD is associated with a complex physical and especially psychic vulnerability based on biological, psychological and environmental factors.

Several studies have found abnormal sensitivity to sensory stimulation in 90% of children (Leekam et al., 2007) and in more than 95% of adults with ASD (Billstedt et al., 2007). Therefore some authors suggest that sensory processing problems are more frequent than social interaction difficulties (Baum et al., 2015).

Problem behaviours

Problem behaviours (PBs or Challenging Behaviours) are common in people with ASD, with a prevalence of 44% (Mattila et al., 2010) which can reach up to 85% in ASD plus ID (McCarthy et al., 2010).

The expression Challenging Behaviour, used for the first time by Emerson in 1995, refers to some abnormal behaviour of a culturally intensity, frequency, and duration as to endanger the physical safety of the person himself and of others, or behaviours that severely limit or prevent access to ordinary services in the community. The term encompasses a series of negative behaviours with respect to the relationship between the individual agent and the surrounding environment. Common types of challenging behaviour include physical and verbal aggressiveness self-directed or directed to other people or objects, oppositional, provocative or impulsive behaviour, escapism, and screams. These behaviours often develop in childhood and persist over time. Frequently the same individual may show multiple forms of challenging behaviour. PBs vary in intensity and frequency and are evaluated for quality (e.g. seriousness of the consequences) and quantity (e.g. the number of times per week and/or the number of times per hour).

Hyper-activity, aggression, self-injurious behaviour, irritability, and tendency to moodiness (Emerson et al., 2001a) are often observed in people with ASD. Challenging behaviour may also simply be a means of communication and occur most likely in individuals with communication impairment (McClean & Grey, 2007; Sigafoos, 2000). Research found a relationship between PBs, such as aggression, tantrums, destruction of property, and severity of communication deficit and socialization problems (Matson, 2009).

The majority of PBs have a complex multifactorial aetiology including biological, psychological, social and developmental factors. Challenging behaviours can occur as symptoms of other psychiatric disorders or physical diseases, but no one particular behaviour can be associated with one specific disorder.

In people with ASD the most frequent causes of PBs are:

• confusion and fear produced by unusual situations or events

• interference with routine or repetitive activities

• inability to understand instructions or explanations

• lack of knowledge on how to behave in a way that is appropriate to the context
• inability to communicate needs and emotions
• sensorial hyperesthesia
• specific phobias of situations or objects
• stress related to the performance of tasks that are too difficult

Determining whether PBs are the result of organic conditions, co-occurrent psychiatric disorders, environmental influences, or a combination of these, is difficult. Thus the assessments procedure should examine all risk factors, to assess appropriate treatment options and to provide support (Matson et al., 2011).

1.3 INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

1.3.1 DEFINITION AND DIAGNOSTIC CRITERIA: EVOLUTION AND CURRENT STATE

ID has a long history within the taxonomy of mental disorders and its conceptualization has always been controversial. In fact, ID is a complex condition, quite hard to define, that include impairments of intelligence, learning, adaptive behaviours, and abilities. ID also occurs early in life and tends to persist for the whole of a person's life.

ID may be considered not as a disease but as a metasyndromic group of health conditions characterized by deficit in cognitive functioning prior to the acquisition of abilities through learning (Salvador-Carulla & Bertelli, 2008). The severity of impairment is characterized by significant ability restrictions or limitations in more activities and interferes with the individual normal functioning. Deficits in intellectual functioning tend to remain stable (APA, 2000); while improvements in adaptive behaviour can occur in which cases the diagnosis of ID may no longer be appropriate (APA, 2013).

Diagnostic classification of ID is complex but appropriate clinical assessments contribute for the estimation of prevalence, health service provision, intervention, and outcomes.

Before the early nineteenth century, societies differed in how or whether they conceptualized ID. Over the past 200 years, the terms used for this condition have included idiocy, deficiency, oligophrenia, mental deficiency, mental handicap, mental subnormality etc. Only recently, older terms such as *mental retardation* has been gradually replaced by *intellectual disability* in an attempt to get away from negative connotations and stigma. The words MR refer to an outdate belief in a general deterioration of mental functions, while ID describes a significantly reduced ability to achieve certain targets. The word ID refers to intelligence and in particular to a deficit of logical-deductive process with a reduced ability to learn new skills.

The term MR is still used by the World Health Organization in the ICD-10 (WHO, 1992) codes, while the APA introduced the term ID although only in the most recent editions of the DSM.

This ambiguity is also summarized by the position of MR in the different editions of the DSM. Firstly both the DSM I (1952) and II (1968) included MR in a section separately from other diagnoses. The DSM III (1980) incorporated MR in Axis I disorders with onset usually occurring in childhood and adolescence. Then the DSM III-R (1987) and DSM IV (1994) moved RM on Axis II along with the personality disorders and PDD, or just with personality disorders, respectively.

By contrast, the American Association for Intellectual and Developmental Disorders (AAIDD) explicitly defines ID as a ‘disability’ and not as a ‘health condition’. Based on the disability perspective, the AAIDD focuses mainly on functioning, adaptive behaviour, and support needs consistent with the model proposed by the ICF. The 11th edition of the AAIDD classification manual was published in 2010 (Schalock et al., 2010).

In the major international diagnostic manuals (DSM-IV-TR and ICD-10), the key feature of MR is a general intellectual functioning which is significantly below average (criterion A) and which is accompanied by significant limitations in adaptive functioning in at least two of the following performance capabilities: communication, personal care, family life, social/interpersonal abilities, use of community resources, self-determination, scholastic skills, work, leisure, health, and safety (Criterion B). Onset must occur before the age of 18 years (Criterion C).

The IQ defines general intellectual functioning or equivalent, obtained by assessment with one or more of the standardized, individually administered intelligence tests (e.g. The Wechsler Intelligence Scale (WAIS), Stanford–Binet Intelligence Scale, or the Kaufman Brief Intelligence Test). Significantly subaverage general intellectual functioning is defined by the APA (2000) as an IQ of approximately 70 or below (approximately 2 standard deviations below the mean).

- Mild mental retardation: IQ level 50-55 to approximately 70
- Moderate mental retardation: IQ level 35-40 to 50-55
- Severe mental retardation: IQ level 20-25 to 35-40
- Profound mental retardation: IQ level below 20 or 25.

Borderline Intellectual Functioning (BIF) is a mild cognitive developmental condition distinguished from ID by less extensive and severe cognitive impairments. BIF is defined as IQ between one and two standard deviations from the population IQ mean that is diagnosed by IQ test score of 70-85. BIF was included in the DSM-IV but omitted from DSM-IV-TR and DSM-5; neither it is included in ICD 10, and ICF (Hassiotis, 2015).

The words *mental retardation*, still available in major international diagnostic manuals, refer to an outdate belief in a general deterioration of mental functions, while *intellectual disability* describes a significantly reduced ability to achieve certain targets. The word ID refers to intelligence and in particular to a deficit of logical-deductive reasoning and reduced ability to learn new skills.

In the DSM-5 (2013) the term MR was officially replaced by ID (Intellectual Developmental Disorder). The term ‘intellectual disability’ corresponds to the term ‘intellectual development disorders’, which has been adopted in the ICD-11 draft. To emphasize an increasing convergence between the two classificatory systems this second term has been reported in brackets in the title of the chapter of the DSM-5.

The new terms adopted by the DSM-5 refer to a disorder with onset in childhood, which includes intellectual and adaptive deficits in the areas of conceptualization, socialization, and practical skills.

In order to make a diagnosis according to DSM-5, the following 3 criteria must be satisfied:

A. Deficit of intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning or learning from experience, and confirmed by both individual clinical assessment and standardized intelligence testing.

B. Deficits in adaptive functioning that failure to meet developmental and socio-cultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning

in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.

C. Onset of intellectual and adaptive deficits during the developmental period.

Although ID/IDD is usually a stable diagnosis, there can be significant variability in cognitive functioning and abilities across different clinical severity levels throughout the life cycle. Therefore, ID is considered a dynamic health condition, and it should be reassessed at key developmental stages, life transitions (e.g. at school entry age, puberty and early and later adulthood), and in case of traumatic events or other life events.

In the DSM-5, the specific age limit of 18 years of age was considered arbitrary. While ID does not require a specific age, individual's symptoms must begin during the developmental period and are diagnosed based on the severity of impairments in adaptive functioning (APA, 2013).

The subaverage general intellectual functioning (Criterion A) is defined by an IQ score of approximately two standard deviations or more below the population mean. When extremely low (under 60) IQ measures are no longer valid.

Therefore, the DSM-5 continues to distinguish four levels of severity (mild, moderate, severe, and very serious), but with different criteria from the DSM-IV and IV-TR. The range of deficits extends from very specific limitations of learning and control of executive functions to a global impairment of social skills or intelligence.

A recent literature mapping indicates that in People with ID (PwID) the same IQ score may be associated with different cognitive profiles, which are also based on the underlying etiopathogenetic factors (Bertelli et al., 2014). For example, persons with Down's syndrome usually manifest impairments in specific areas of language, long-term memory and motor performance while showing relative strengths in visuospatial construction (Edgin et al., 2010).

The term adaptive behaviour refers to the individual's ability to cope with and meet environmental demands for personal independence and responsibility (APA, 2013) according to the expectations of their chronological age and cultural group (Schalock et al., 2010).

The DSM-5 defines the severity levels on the basis of adaptive functioning and not on IQ scores because it is the adaptive functioning in the areas of conceptualization, socialization, and practical skills that determine the level of support required to maintain an acceptable condition of life.

Measurable indicators of adaptive functioning include the following:

- Conceptual skills: language, reading and writing, using money, understanding and using concepts such as time, numbers or measures, and problem solving.
- Social skills: creating and maintaining mutually satisfying social relationships, interactions with others, social engagement and participation, emotional competence, social problem solving, self-direction, responsibility, gullibility and naïveté, and self-esteem.
- Practical skills: instrumental and basic activities of daily living, work/vocational skills, domestic skills, and personal hygiene.

The debate on ID classification could have serious implications. Diagnostic categories are used throughout the world to specify which people are eligible for what health care, educational and social services. Therefore the location of ID as *disability* or *health conditions* would impact on health

statistics, health policy, and on the services available to this vulnerable population (Salvador-Carulla et al., 2011).

1.3.2 EPIDEMIOLOGY

The prevalence of ID is estimated between 1 and 3%, and the incidence is estimated to be around 1.8% (Heikura et al., 2003; Harris, 2006). In developed countries like Finland or the Netherlands, the prevalence of ID is currently less than 1%, while it may rise to 4–5% in more deprived regions of the world (Durkin, 2002) and can reach up to 6% in some countries in Eastern Europe. Among the four different severity degrees, 85% have mild ID, 10% moderate, 4% severe, and 2% profound (King et al., 2009).

Mild ID is present in 80 to 85% of the world's population (Schalock et al., 2010), that could explain why many person with ID are not identified until they reach school age and start having difficulties acquiring and learning new skills.

The prevalence of BIF is estimated between 12.3%; Hassiotis et al. (2008) found that on a sample of 8.450 adults living as part of a family in UK, approximately one-eighth had BIF.

The prevalence of ID is higher in males than female in both adults, and children/adolescents. Among adults the male-to-female ratio varied between 0.7 and 0.9 (Maulik et al., 2011).

The lack of adequate and consistent epidemiological data was one of the main reasons for the exclusion of the last study conducted by the World Health Organization and the World Bank Burden of Disease. One consequence is that ID still occupies an important position among the 'hidden problems' of global health. Another consequence is that the gap between the offering of health services and the unmet needs of intellectually-disabled people has become incalculable (WHO, 2007).

1.3.3 ETIOPATHOGENESIS

IDs are a heterogeneous group caused by a different combination of specific causative factors, both genetic and environmental (Bertelli & Kishore, 2014). The cause is unknown for up to 60% of cases (Rauch et al., 2006).

Prenatal causes

Genetic factors

A proportion of cases ranging from 17% to 50% are caused by a genetic disorder (Moeschler & Shevell, 2006; Rauch et al., 2006; Tzschach & Ropers, 2007; Kaufman et al., 2010), while non-syndromic ID account for 30-50% of cases (Daily et al., 2000; Gonzáles et al., 2013).

Conventionally, genetic forms of MR are divided into two major categories: syndromic MR characterized by associated clinical, radiological, metabolic or biological features, and non-syndromic forms in which cognitive impairment represents the only manifestation of the disease. Although this

distinction remains useful for clinical approach, recent studies and detailed clinical follow-up indicated that distinctions between syndromic and non-syndromic MR are disappearing, and some of the latter could be recognized as syndromic forms (Chelly & Mandel, 2001; Frints, et al 2002; Ropers & Hamel, 2005).

Detailed analyses of database and literature searches reveals more than a thousand of genes can cause MR. Furthermore, more than 290 genes are involved in clinical phenotypes, metabolic, and neurological disorders associated with MR (Kahler & Fahey, 2003; Chelly et al., 2006; Levy, 2009). Trisomy 21 is the chromosome abnormality responsible for over 95% of Down's syndrome, which is the best-known genetic cause of MR (Patterson & Costa, 2005; Rauch et al., 2006).

The most prevalent genetic conditions include Fragile X syndrome (Leonard & Wen, 2002), Turner syndrome, Klinefelter's syndrome (Money, 1993), neurofibromatosis (or von Recklinghausen's disease), phenylketonuria, Williams's syndrome, and Prader-Willi syndrome. ID occur in other genetic syndromes like tuberous sclerosis, Huntington's disease (Mouridsen & Sorensen, 1995; Raznahan et al., 2007), mucopolysaccharidosis, alcaptonuria, and porphyria (Kahler & Fahey, 2003; Levy, 2009)

The risk of transmission of recessive genes is greatly increased by consanguineous marriage. For a couple of first cousins, the chance of passing on chromosomal alterations is about 5 times higher than for couple that are not blood relatives (Ten Kate, 2012).

Idiopathic ID supports the hypothesis that rare *de novo* point mutations can be significant causal factors of MR (de Ligt et al., 2012). Microarray studies, and exome sequencing techniques found CNVs in approximately 15% of PwID (Ropers & Hamel 2005; Pfundt & Veltman, 2012).

Studies observed that recurrent CNVs involve the following genes: 1q21.1, 1q41-42, 2p15-q16.1, 3q29, 7q11.23, 9q22.3, 12q14, 14q112, 15q13.3, 15q24, 16p11.2, 16p11.2-12.2, 16p13.1, 17p11.2, 17q21.31, 19q13.11, 22q11.2, and Xq28 (Vissers et al., 2009; Morrow, 2010).

Berkel and colleagues (2010) observed de novo CNVs of the SHANK2 gene in 184 individuals with ID, and in 396 individuals with ASD. CNVs of the NLGN4 gene and 16p11.2 were identified both in ID and ASD (Berkel et al. 2010; Cook & Scherer, 2008; Fernandez et al., 2010), while deletions of the 1q21.1 region were detected also in schizophrenia (Stone et al., 2008).

Epigenetic mechanisms

Epigenetic regulation has been implicated in the causation of ID. Mutations in Methyl CpG binding protein 2 (MeCP2) and ATP-dependent helicase X-linked (ATRX) protein gene is already well established in Rett syndrome, Down's syndrome and some cases of X-linked (Dragich et al. 2000; Gibbons et al. 2009; Nan et al., 2007; Sanchez-Mut et al., 2012).

However, in most cases such modifications are known to be affected by environmental factors before and after birth (Zahir & Brown, 2011).

Biological and environmental factors

Prenatal causes of ID include congenital infections such as cytomegalovirus, toxoplasmosis, herpes, rubella, influenza and human immunodeficiency virus (Strømme & Hagberg, 2007). The human foetus seems unable to produce an effective immunological response in early pregnancy; the ability of children to produce antibodies increases significantly only between the sixth and twelve months of age.

Exposure to pollutants, heavy metals, and harmful medications such as thalidomide, phenytoin and warfarin in early pregnancy; additive substances such as alcohol, nicotine and cocaine can also cause MR (Daily et al., 2000; Ke & Liu, 2012; Sithisarn et al., 2012; Behnke & Smith, 2013).

Other prenatal risk factors are: maternal hypoglycaemia, diabetes and malnutrition (Mann et al., 2013; Groce et al., 2014). Evidences from experimental studies show that malnutrition in utero can impact on brain development process leading to reduce nervous cells, protein synthesis defect, and abnormal electrical activity (Nyaradi et al., 2013).

Perinatal causes

Perinatal causes involve complications in delivery, severe prematurity, very low birth weight, birth asphyxia, and birth trauma. Furthermore neonatal complications in the first 4 weeks of life included septicaemia, severe jaundice, and hypoglycaemia (Nosarti et al., 2004; Kolevzon et al., 2007).

Low birth weight at term delivery can be due to genetic causes. In other cases poor nutritional contribution in uterus associated with placental insufficiency, or others damaging agents may occur. These children, born small for gestational age, show retardation in foetal growth and subsequent neurological complications that are different to those related to shorter gestation period. True pre-term births before 26 weeks of gestation and pre-term births after less than 36 weeks of gestation are those at greatest risk of developing neurological damage, which increases in inverse proportion to their degree of maturity and birth weight (<1500 grams) (Winter, et al., 2002; Marlow et al., 2005). Structural abnormalities of the CNS were more common among children born at lower limit of viability and birth weight, while learning disabilities affect almost exclusively children of lower socioeconomic status. This finding supports the theory that, independently to biological factors, adverse childhood events have a negative effect on cognitive performance (Ritchie et al., 2010).

Postnatal causes

During the postnatal period, which includes infancy and childhood, brain infections such as encephalitis, and bacterial meningitis are observed (Noyola et al., 2001). Furthermore, encephalic traumatism, chronic lead exposure, severe and prolonged malnutrition can lead to some kind of ID (Leonard & Wen, 2002; Anderson et al., 2005). Malnutrition is a common cause of lower cognitive abilities (Durkin et al., 2000). The effects of malnutrition on the development of ID are almost always concomitant with negative socio-environmental conditions. Studies reported a significant association

between ID and exposure to a wide range of environmental and psychosocial distress including infections, inadequate caregivers, low level of stimulation, and social deprivation (Leonard et al., 2005; Emerson, 2007).

Neuroanatomical abnormalities

Structural abnormalities of the CNS are the result of a multitude of insults that are primarily prenatal in origin. Primary malformations such as neural tube defects, cerebral dysgenesis, and congenital hydrocephaly or hydranencephaly can all be associated with severe ID.

PwID show extensive damage in the integrity of the brain's structures, and wide cerebral abnormalities are positive associated with greater cognitive dysfunction (Plomin & Kosslyn, 2001; McDaniel, 2005). Cortical grey matter volumes is related to cognitive performance such as planning, working memory, and attention. Studies found negative correlations between low IQ and reduced total volume of frontal grey matter (Reiss et al., 1996; Sowell et al., 2001), particularly in the orbitofrontal and medial frontal regions (Frangou et al., 2004).

Also the integrity of white matter tracts, including the corpus callosum, cingulum, uncinate fasciculus, corticospinal tract and optic radiation, are damaged in people with MR (Yu et al., 2008).

The corpus callosum is the major white matter tract that connects the right and left cerebral hemispheres. Studies found thinning or reduced size of the corpus callosum, particularly in anterior subregions (Njiokiktjien et al., 1994; Spencer et al., 2005). It is involved in the control of sustained attention and adaptive skills during complex cognitive tasks (Colom et al., 2006). Researchers found a significant left-greater-than-right asymmetry of the cingulum, which is associated with impairment of the executive functioning (Gong et al., 2005). Abnormalities of the uncinate fasciculus are related with deficit in verbal, visual memory, and executive performance (Levine et al., 1998), while the corticospinal tract plays a role in the control of discrete finger movements (Martin, 2005).

The optic radiation or geniculo-calcarine tract transmits visual information. PwID seem to have a high prevalence of visual impairments (Warburg, 2001), which leads to sensorial problems, such as strabismus, loss of visual acuity, and amblyopia (Atkinson et al., 2001).

1.3.4 PROBLEMS ASSOCIATED WITH INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

The comorbidity with organic pathology in persons with ID is much higher than in the general population. The most frequent disorders are: epilepsy, gastro-oesophageal reflux disorder (GORD), constipation, visual impairments, hearing impairments, osteoporosis, respiratory infection, risk of aspiration and choking, and repeated accidents or falls. Diabetes is more than twice common in PwID as in the general population, and obesity is significantly associated with diabetes.

Specific genetic conditions such as Down’s syndrome or William’s syndrome are associated with illnesses as thyroid disorders, and cardiovascular disease, which may arise at different stages of life.

Also antipsychotic medications seem to contribute to physical diseases (Jansen et al., 2004; Prasher & Janicki, 2008).

Organic pathologies are often undetected and misinterpreted as apparent PBs, or psychiatric symptoms. Therefore, in the complex evaluation of PwID it is essential to consider all factors that can influence behaviour, and affect vulnerability and symptom presentation.

Problem behaviours

PBs are very common in adults with ID with a prevalence ranging from 5 to 60%, and a point prevalence of about 20%, depending on the exact definition of the terms used (Emerson et al., 1999; Smiley, 2005; Cooper et al., 2007c; Deb et al., 2008).

The most common type of PBs in this population are: physically aggressive behaviour, verbally aggressive behaviour, screaming, destructive behaviour or aggression to property, self-injurious behaviour, overly-demanding behaviour, oppositional-defiant behaviour, and sexually inappropriate behaviour (Lowe et al., 2007; Smith & Matson, 2010b). Behavioural difficulties often persist, with relapse and remit, and the same individual may show multiple forms of challenging behaviour (Lowe et al., 2007).

PBs result from the complex interaction between biological, psychological, social and developmental factors (Griffith & Gardner, 2002), whereas in some cases genetic causes underlie PBs and impacts directly on the phenotypic expression (O'Brien & Yule, 1995).

Challenging behaviours can occur as symptoms of other psychiatric or physical disorders (Moss et al., 2000; Emerson et al., 2001b; Kishore et al., 2005; Hemmings et al., 2006; Felce et al., 2009; De Winter et al., 2011), especially in individuals with more severe impairment (Felce et al., 2009). In this case, before making a diagnosis is required to clarify the temporal relationship to the onset of the PBs (Charlot, 2005). Hence a special focus is needed on assessment of challenging behaviours in ID, as they are a major cause of misdiagnosis, inadequate treatment, and service use in this population group.

1.4 SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS

1.4.1 DEFINITION AND DIAGNOSTIC CRITERIA: EVOLUTION AND CURRENT STATE

Schizophrenia is a complex psychiatric disorder with a chronic course characterized by the presence of some, but not necessarily all, of the following features: emotional blunting, cognitive impairment, social isolation, disorganized speech and behaviour, delusions, and hallucinations.

Since its first conceptualisation the disorder has been one of the most studied and discussed psychiatric disorders.

The concept of schizophrenia originates from the description by Emil Kraepelin (1856-1926), more than a century ago. Kraepelin, based on his observations of many clinical cases, believed that the illness occurred in young people and that it inevitably led to severe cognitive deterioration and altered pattern of behaviours. His observations led him to integrate different clinical pictures into a single nosological entity under the term of 'dementia praecox'. Kraepelin combined hebephrenia, catatonia, which were previously described by Hecker and Kahlbaum respectively, and paranoid states into the concept of dementia praecox.

Kraepelin's concept of schizophrenia was significantly modified by Eugen Bleuler (1857-1939). He observed some clinical cases, which did not evolve into deterioration, that previously was considered as key feature by Kraepelin. Bleuler coined the term 'schizophrenia' to replace 'dementia praecox' and highlight that the deficit in integration of different psychic functions (personality, thought, memory and perception) was the distinctive feature (Altamura et al., 2014). The age of onset and course were considered less significant symptoms. Bleuler introduced a fundamental distinction between obligatory and accessory symptoms of schizophrenia diagnosis. The basic symptoms, which are known as the '4 A of Bleuler' included thought and speech derailment (*loosening of Associations*), volitional indeterminacy (*Ambivalence*), *Affective incongruence*, and withdrawal from reality (*Autism*). The accessory symptoms included delusions and hallucinations, which are commonly classified as 'positive' symptoms (Jablensky, 2010; Tandon, 2012).

The history of this disorder is complex and the concept of schizophrenia has undergone several revisions over the years. All the definitions of schizophrenia included three major clusters of features: the Kraepelinian stress on avolition, chronic course, and poor outcome (Kraepelin, 1971); the Bleulerian accent on negative symptoms and dissociative pathology (Bleuler, 1950); and the Schneiderian emphasis on positive symptoms (Schneider, 1959) (Tandon et al., 2013).

Symptoms of schizophrenia were classified by Kurt Schneider (1887–1967) in 1938. 'First-rank' symptoms, considered by Schneider to be the most important indicators of schizophrenia, include the experience of thought alienation (e.g. thought insertion, thought withdrawal, thought broadcast), somatic passivity, delusional perception, and auditory hallucinations in the form of voices discussing, commentary, and repeating. 'Second-rank' symptoms are symptoms of schizophrenia but often occur with other mental disorders. They include perplexity, emotional blunting, depressive and euphoric

mood changes, sudden delusions (e.g. delusions of reference, paranoid delusion, persecutory delusion), and other disorders of perception.

The accent on one or another of the major three perspectives has changed over time (Andreasen, 1989; Bruijnzeel & Tandon, 2011; Keller et al., 2011a). In the DSM-I and DSM-II the definition of schizophrenia reflected the Bleulerian view.

In the 1970s the discrepancy between the international nosographic systems (DSM and ICD) was evident, leading to more diagnostic disagreement in USA and Europe (Kendell et al., 1971; Wing & Nixon, 1975). Additionally, over the course of the decades, a number of European and American clinicians proposed further subnosological distinctions within the widening phenotype of schizophrenia, including schizoaffective disorder, schizophreniform psychoses, paranoid non-paranoid schizophrenia, and schizoid personality.

In the 1980s, The DSM-III attempted to define a more homogeneous disorder by requiring a triad of symptoms characterized by chronic course, poor functioning and Schneiderian first-rank symptoms.

From DSM-III through DSM-III-R to DSM-IV, there were few changes of the criteria of schizophrenia with the elimination of the requirement that onset occur before age 45 and inclusion of negative symptoms.

In the last 1980s the gap between the DSM-IV and the ICD-10 definitions of schizophrenia remained. Whereas the DSM-IV required a total duration of symptoms at least of 6 months and social/occupational dysfunctions, the ICD-10 required a minimum duration of 1 month and has no the requirement for social/occupational dysfunction. Furthermore, the ICD-10 lays greater focus on the Schneiderian first-rank symptoms than the DSM-IV. In contrast to the DSM, the ICD-10 also defines two additional subtypes - post-schizophrenic depression and schizophrenia simplex, where the latter was a type of schizophrenia with progressive development of negative symptoms and no history of psychotic episodes.

In the last edition of the DSM (DSM-5; APA, 2013) the definition of schizophrenia remained essentially the same as that specified by the DSM-IV-TR, but the DSM-5 makes a number of changes. The DSM-5 added the word ‘spectrum’ to the title. This new term Schizophrenia Spectrum and other psychotic Disorders (SSD) implies that there are different degrees of the disorder.

The six diagnostic criteria (A–F) of the DSM-IV-TR were retained and modest changes were made. In criterion A, the definition of negative symptoms was refined, and the requirement that at least one characteristic symptom must be delusion, hallucination, or disorganized speech was inserted.

According to the DSM-5 to meet the criteria for diagnosis of SSD, the patient must have experienced at least 2 of the following symptoms (A), each present for a significant portion of time during a 1-month period (or less if successfully treated). At least 1 of the symptoms must be the presence of delusions, hallucinations, or disorganized speech:

A. 1. Delusions. (Delusions can take a number of different forms: paranoid delusions or delusions of persecution, delusions of reference somatic delusions, delusions of grandeur)

2. Hallucinations. (They can be: visual auditory tactile olfactory gustatory experiences)

3. Disorganized speech (e.g., frequent derailment or incoherence)

4. Grossly disorganized or catatonic behavior.

5. Negative symptoms (i.e., diminished emotional expression or avolition). Some of these include: lack of emotion, low energy, lack of interest, low motivation, affective flattening alogia, inappropriate social skills or lack of interest or ability to socialize with other people, and social isolation.

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relationships, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less, if successfully treated) that meet Criterion A (e.g., active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbances may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Whereas the DSM-IV-TR included paranoid, disorganized, catatonic, undifferentiated and residual subtype of schizophrenia, the APA removed the schizophrenia subtypes from the DSM-5; they did not appear to be helpful for providing better-targeted treatment or predicting response to treatment. Also catatonia is no longer associated with schizophrenia (Heckers et al., 2009). Special treatment of bizarre delusions and Schneider's first-rank symptoms was also removed.

The DSM-5 included a set of course specifiers that provide information on the cross-sectional state and longitudinal courses of SSD. The distinction of course specifiers according to their current state and its longitudinal progress allows the clinician to document both the current status and the previous course up to the present observation period (Tandon et al., 2013).

However, the debate on the SSD diagnostic symptoms is still in vigour.

Evidence shows that cognitive deficits are a significant psychopathological feature of SSD. The hypothesis of the presence of cognitive dysfunction in people with schizophrenia dates back to the constitution of modern psychiatry, when Kraepelin conceptualized the disorder as dementia praecox. This theory has received limited credit for a long time, although the clinicians have continued to recognize that in people with MR there is an increased vulnerability (psychosis of engagement). Only in the last twenty years, on the basis of the progressive affirmation of pathogenic models pertaining to

neurodevelopment, identification and treatment of cognitive deficits has been a subject of renewed interest.

Although the inclusion of cognitive impairment in the diagnostic criteria of schizophrenia was considered (Keefe, 2008; Tandon & Maj, 2008), no change was made. In fact, cognitive deficit has not been considered sufficiently precise to distinguish between schizophrenia and other disorders (Depp et al., 2007; Reichenberg et al., 2008; Barch, 2009; Reichenberg, 2010). The cognitive symptoms of schizophrenia refer particularly to concentration and memory problems (Trivedi, 2006; Keefe & Harvey, 2012). These impairments can include disorganized thinking, slow thinking, difficulty understanding, poor concentration, poor memory, difficulty expressing thoughts, and difficulty integrating thoughts, feelings, and behaviour. On this subject, cognitive rehabilitation programs have generated consistent interest (Wykes & Spaulding, 2011; Barlati et al., 2012).

1.4.2 EPIDEMIOLOGY

Lifetime prevalence of schizophrenia is about 1%, varying from 0.5% to 1.5%. The incidence is approximately 1.5/10.000 (Owen et al., 2004; McGrath et al., 2008). The average age of onset is typically in late adolescence or early adulthood (Van Os & Kapur, 2009). A minority of patients has age of onset in middle or old age after 40-60 years (Howard et al., 2000). Furthermore childhood-onset schizophrenia is very rare and usually occurs after the age of 5 years (Kumra et al., 2001).

Evidence suggests that schizophrenia is more common in men than in women and the male-to-female ratio varied between 1.3 and 1.4 (McGrath et al., 2004; Aleman et al., 2003).

1.4.3 ETIOPATHOGENESIS

Schizophrenia is a disorder with variable phenotypic expression that results from a complex set of interrelated causal factors, including genetic, as well as environmental contributions (Jablensky & Kalaydjieva, 2003; Mäki et al., 2005; Rapoport et al., 2005).

Genetic factors

Familial predisposition and genetic risk factors for SSD has been observed. Although over two-thirds of cases occur sporadically, having an affected family member is associated with an increased risk of developing schizophrenia. Twin studies have found the heritability of risk about of 65-80%. Researches have consistently estimated concordance rates of 41-65% in monozygotic and 28% in dizygotic twins (Cardno & Gottesman, 2000; Sullivan et al., 2003). The absence of a complete concordance in monozygotic twins, which share the entire gene pool, indicates that further factors other than genetic ones should be taken into account in the pathogenesis of disease.

The risk increases with the degree of biological relatedness to the patient (Kendler & Diehl, 1993). Studies reported increased frequency of parental consanguinity among patients with schizophrenia. First cousins show a risk of 2% that their offspring developing schizophrenia, while the risk in the

general population is about 1%. The offspring of two schizophrenic parents show a risk of 50%, and the offspring of one schizophrenic parent show a risk of 13% (Jablensky, 2000; Tsuang, 2000; Gottesman & Erlenmeyer-Kimling, 2001).

The first investigations on the molecular genetic of schizophrenia date back to the late 1980s. Since then, numerous studies have been conducted using both candidate genes for the coding of protein in neurotransmitter systems with possible roles in the pathogenesis of schizophrenia and systematic investigations into the entire human genome. Combinations of variations in multiple genes are associated with schizophrenia with a proportion of the transmitted genotypes remaining clinically unexpressed (Muir et al., 2006).

Recently, large-scale studies have considerably advanced in terms of identifying risk genomic regions. Over 100 loci are now associated with schizophrenia as identified by Single Nucleotide Polymorphisms (SNPs) in genome-wide association studies. The Psychiatric Genetics Consortium (PGC) attempted to combine findings from the Genome-Wide Association Studies (GWAS) of schizophrenia. In 2014 this collaboration expanded the data into the largest meta-analysis on GWAS data (36.989 cases and 113.075 controls), indicating 108 schizophrenia-associated genetic loci, 83 of which have not been previously described (Ripke et al., 2014).

Other studies have suggested that high risk-rare variants, which could be caused by de novo mutations and CNVs, are linked to increased risk for schizophrenia and other neurodevelopmental disorders (Malhotra & Sebat, 2012). Reviews have listed some genes including: NRG1 (neuroregulin 1), DTNBP1 (dysbindin), DRD1-4 (dopamine receptors D1–D4), NRXN1 (neurexins), COMT (catechol-O-methyl-transferase) and GRM3 (metabotropic glutamate receptor) (Talkowski et al., 2008; St Clair, 2009; Bassett et al., 2010; Magri et al., 2010; Girirajan et al., 2012; Kukshal et al., 2013).

The pathogenic effects of these CNVs are not limited to schizophrenia; many increase risk for other disorders such as ID and ASD (Girirajan et al., 2012; Malhotra & Sebat, 2012).

An updated meta-analysis on CNVs for schizophrenia published in 2015 expanded the number of CNVs implicated in schizophrenia, replicated previous findings for disruption of glutamatergic signalling, and has also offered the first genetic evidence for the involvement of GABAergic neurotransmission deficit (Pocklington et al., 2015).

Neurotransmitters system

In the second half of the twentieth century, dopamine (DA) dysfunction was considered to play a crucial role in the pathogenesis of schizophrenia. This was firstly due to studies on DA-releasing drugs, such as amphetamine, which induce psychosis and also to evidences that antipsychotic drugs block the dopaminergic D2 receptors (Carlsson, 1988; Howes & Kapur, 2009).

Recently, studies showed that mutations in the gene coding for the serine/threonine protein kinase (AKT) which mediates the dopaminergic neurotransmission, plays an important role in the pathogenesis of schizophrenia (Arguello & Gogos, 2008; Zheng et al., 2012; Emamian, 2012).

Later researches suggest that excessive DA function cannot fully explained schizophrenia. Studies on cognitive impairments have led to consideration that other neurotransmitters, such as glutamate, may play a role (Javitt, 2010; Lau et al., 2013). Cognitive symptoms including attentional impairment and memory deficits may result from a decreased activity of the N-methyl d-aspartate (NMDA) receptor on GABA inhibitory interneurons in the prefrontal cortex (Kraguljac et al., 2012; Plitman et al., 2014). In a large-scale study conducted by the Consortium on the Genetics of Schizophrenia, the organization noted that NMDA receptor NR1, NR2A, and NR2B subunits polymorphisms are often associated with the diagnosis of schizophrenia. Through further research a relevant association with NMDA subunits alteration has been identified also for ASD (Endele et al., 2010; Hamdan et al., 2011; Saunders et al., 2012). In addition, recent work for the SHANK3, NLGN1, NRXN1, FMRP1, MeCP2, DISC1, RELN on transgenic mice genes and rodents exposed in utero, respectively considered models of autism and autism risk, showed a reduced activity of the NMDA receptor signaling. Harmful mutations of NR1, NR2A, and NR2B have been identified through large-scale studies, also in PwID (Coyle, 2006; Insel, 2010). Considering all of the data, these results indicate that a dysfunction of NMDA receptor signaling may represent a molecular substrate common to several neuropsychiatric disorders of development.

Finally, serotonin system alterations also seem to contribute in the pathogenesis of schizophrenia through a dysfunction of the dopaminergic modulation (Abi-Dargham, 2007; Selvaraj et al., 2014).

Epigenetic mechanisms

Epigenetic regulators of gene expression including DNA cytosine methylation, posttranslational histone modifications, and chromosomal looping for promoter-enhancer interactions, seem to contribute to altered expression of genes related to synapse and metabolism in schizophrenia (Roth et al., 2009; Akbarian, 2014; Shorter & Miller, 2015). For example, in the prefrontal cortex of subjects with schizophrenia, abnormal DNA or histone methylation at sites of specific genes and promoters can lead to changes in RNA expression. These findings are of interest from a neurodevelopmental perspective because there is increasing evidence that epigenetic regulation of genes are highly involved during the first years of life.

Biological factors

Brain hypoxia before at or immediately after birth, low birth weight, and small head circumference are associated with an increased risk of developing schizophrenia. Furthermore, pregnancy bleeding, preeclampsia, diabetes, rhesus incompatibility, and delivery complications were also associated with schizophrenia (Cannon et al., 2002; Abel et al., 2010).

Exposure to toxins and viral infections in utero, especially during the second trimester, or in childhood are significant risk factors for schizophrenia. Polio, varicella-zoster, rubella, herpes simplex virus,

influenza and Toxoplasma gondii have been correlated with the later development of schizophrenia (Venables et al., 2007; Boksa, 2008).

Recent findings support the hypothesis that schizophrenia is associated with alterations of the tryptophane-kynurenine metabolic pathway due to activation of specific parts of the immune system (Müller et al., 2015). Therefore, the immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia disorder (Müller & Schwarz, 2006).

Environmental factors

Childhood experiences of social adversity, social exclusion, migration, and abuses have been suggested to contribute to schizophrenia (Boydell et al., 2004; Wicks et al. 2005).

A study found that chronic adverse exposures may produce sensitization and hyper reactivity of the dopaminergic system at high levels (Pruessner et al., 2004).

There is evidence that living in an urban area has repeatedly is a risk factor for developing schizophrenia (Krabbeddam, 2005), even after controlling for other factors such as drug use (van Os, 2004). The likelihood of being diagnosed with the schizophrenia was found to increase with the number of years spent in an urban environment in childhood and adolescence (Pedersen et al., 2001). Various possible explanations have been hypothesized including infectious causes and social exclusion which interact with genetic vulnerability (Kelly et al., 2010).

Strong evidence indicates that drugs such as cannabis, amphetamines, and hallucinogens may trigger psychotic relapse and precipitate schizophrenia in vulnerable individuals (Meltzer & Fatemi, 2000; Arsenault et al., 2004).

Neuroanatomical abnormalities

The most common findings on examination by computed tomography and Magnetic Resonance Imaging (MRI) in patients with schizophrenia have been enlarged size of the cerebral ventricles, white matter anisotropy, and decreased cerebral cortical volume especially in the temporal lobe, superior temporal gyrus, and insula (Honea et al., 2005; Bakhshi & Chance, 2015).

Individuals who developed psychosis were found to have reduced grey matter volume in the right medial temporal, lateral temporal, inferior frontal cortex, and in the cingulate cortex, bilaterally (Pantelis, et al., 2003). Other neuroimaging studies confirm that cerebral structures including the cavum septi pellucidi, amygdaloid/hippocampal complex, basal ganglia, thalamus, and cerebellum play a role in the SSD symptoms (Shenton et al., 2001).

Reduction in whole brain and gray matter volumes were associated with lower premorbid IQ and poorer performance on IQ test scores (Antonova, 2005).

Patients with schizophrenia show a broad spectrum of cognitive dysfunctions and include problems in sustaining attention, performing executive functions, verbal and visuo-spatial working memory and language skills, each of which is associated with different brain structures (Riley et al., 2000). The

enlargement of the third ventricle seems to correlate with deficits in abstraction, language, and attention. Damage to the prefrontal cortex was associated with impaired executive functions (Orellana & Slachevsky, 2013). Abnormalities of the temporal lobe were related to cognitive deficits in processing speed and performance accuracy; damages to the hippocampus were associated with memory and executive function impairment, and anomalies of the parahippocampal gyrus were related to deficient abstraction ability (Antonova et al., 2004, 2005).

Premorbid IQ

Cognitive deficits affect the vast majority of schizophrenia patients, with prevalence estimates that averaged about 75-80% of the patient population and a quantification that was between 1 to 2 standard deviations below the mean of the average population (Woodberry et al., 2008; Morgan, 2008). A meta-analysis conducted by Heinrichs and Zakzanis (1998) of 204 studies comparing a total of 7.420 patients with schizophrenia and 5.865 healthy controls showed a deterioration of global cognitive functioning with a very significant effect size. Systematic reviews more recently have shown a similar deterioration in people with the first episode of the illness, in those never treated with antipsychotic drugs or those in remission of symptoms (Heaton et al., 2001; Bowie et al., 2006; Forbes et al., 2009; Mesholam-Gately et al., 2009).

Schizophrenia has been consistently associated with a range of intellectual impairments, such as attention, language and memory deficit, some of which precede the onset of psychotic symptoms.

The cognitive impairments that are most frequently encountered are:

- Reduction of intelligence quotient (IQ), already observed in children who later develop the disease and more clearly with the onset of the disorder, to be able to present a substantially stable course;
- Attention deficits, in particular the responsiveness to sensory stimuli;
- Deficits in working memory;
- Deficits in verbal memory, immediate and delayed;
- Deficits in executive functioning, with particular difficulty in categorizing information and errors in preservation.

Evidences suggest that the risk of schizophrenia increases by 3.7% for every point decrease in IQ (Khandaker et al., 2011). Greater premorbid IQ decrement, which affects both verbal and non-verbal cognitive abilities, has been associated with increased severity of illness and earlier onset of schizophrenia (Cornblatt et al., 2003).

Premorbid low IQ indicates that impairment in intellectual ability may exist from early in life and is not just a consequence of the pathological process of disease. In fact, poor school performance in childhood can be considered as premorbid sign for the later development of schizophrenia (Isohanni et al., 2004).

1.4.4 PROBLEMS ASSOCIATED WITH SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS

Schizophrenia is a serious brain disorder that distorts the way a person thinks, perceives reality, and relates to others, which led to have problems functioning in society, and in relationships.

People with schizophrenia have a wide range of multiple-comorbid physical-health problems and are at high risk of premature mortality due to cardiovascular disease, diabetes, obesity and smoking-related lung disease (Smith et al., 2013). Metabolic syndrome occurs frequently in schizophrenic patient, with prevalence two to three time higher than in the general population. Metabolic syndrome is a cluster of metabolic including obesity, hypertension, cardiovascular diseases, dyslipidemia, hyperuricemia, abnormalities of glucose homeostasis and diabetes mellitus (De Hert et al., 2009). Unhealthy lifestyles, restricted access to health care, social services or the side effects of antipsychotic drugs may contribute to its development (Ryan & Thakore, 2002).

Problems behaviours

The prevalence rates of violent behaviours in people with schizophrenia shows a wide variability ranging from 10 and 15% (Fazel et al., 2009). There was a common and widespread view that schizophrenic patients were violent. However, studies showed that these patients are not inclined to violence, but they often prefer stay alone and tend not to be disposed to social relations (Brüne et al., 2011). The risk of violent behaviours increased when these patients are under the influence of alcohol or psychoactive substances. Furthermore, people with paranoid and psychotic symptoms, which can become worse if antipsychotic drugs are discontinued, may also be at higher risk for violent behaviours (Buchanan et al., 2002; Hodgins, 2008; Wehring & Carpenter, 2011).

Suicide and suicide attempts amongst schizophrenics are 8.5 higher than in the general population. Estimates suggest that 10% of patients with schizophrenia complete suicide (Siris, 2001). Furthermore a high percentage, ranging between 20 and 50%, have a history of suicide attempts in the course of disease and in particular in the psychotic acute phase (Meltzer, 2006). Study shows that suicidal behaviours are also more likely to occur in people with early onset psychosis, alcohol abuse, substance dependence, feelings of loneliness, and low compliance to treatments (Mork et al., 2012).

1.5. PSYCHIATRIC COMORBIDITY

1.5.1 GENERAL ISSUES

In PwID, the prevalence of mental disorders is up to four times higher than in the general population (Cooper et al., 2007c). However, the opinion that psychiatric disorders could not occur in PwID has represented the view of the majority of the scientific community for a long time. Various explanations were given, including a lack of consensus on which problems in ID should be considered as mental health problems (Holland & Koot, 1998). The long-lasting denial of the presence of psychiatric disorders in PwID was a significant impediment to research on the specific phenomenological and psychopathological concepts, and to the development of effective assessment procedures. Thus, the nature of psychiatric disorders, and what causes them often remained unresolved.

Noteworthy, the DSM-III and DSM-IV included MR on Axis II along with the personality disorders, while 'major' groups of diagnosis (depression, psychosis, etc.) were placed on Axis I. This choice had several implications. The placement of psychiatric disorders and MR on a separate axis may prevent the effect of 'diagnostic overshadowing' (Reiss et al., 1982), which is the difficulty to attribute the observed or referred dysfunctions to the basic condition of ID or to a comorbid psychiatric disorder (Reiss et al., 1982; Reiss & Syszko, 1983; Deb et al., 2001b; Jopp et al., 2001). This categorization could avoid the tendency of clinicians engaged in evaluations of MR to focus almost exclusively on intellectual and adaptive functioning, ignoring other important information on overall mental health. However this separation may result in the opposite effect, reducing the impact of MR on the psychopathology and clinical presentation.

The assessment of psychiatric disorders in PwID requires appropriate modifications in respect to the general population, in order to adapt for cognitive impairments, language limitations, communication problems, sensory dysfunctions, skill difficulties, adaptation deficits, and physical disabilities that are frequently in this population. Moreover, some studies underline the interference of PBs in the psychiatric diagnostic evaluation (Reiss et al., 1982; Reiss & Syszko, 1983). All these difficulties creates diagnostic challenges for clinicians who did not receive any specific training to diagnose psychiatric disorders in PwID (Werner & Stawsky, 2012). The 'diagnostic overshadowing' represents the first problem. Furthermore, mainly in the most severe cases, some individuals may show 'cognitive distortion' (Sovner & DesNoyers Hurley, 1986), which consists of difficulties in introspection capacity, in defining one's own life experiences, and in communicating states of uneasiness or suffering (Cooper et al., 2003). PwID may have poor verbal expression capacities, may be passive, inclined to acquiescence and, for certain peculiarities in the experiential range, may show deviations from the norm according to the attribution of meaning to communicative contents ('psychosocial masking'; Sovner, 1986). The developmental level, previous life experiences, cultural, and environmental influences impact on the presentation of symptoms, which often is atypical, chaotic, intermittent, fluctuating, masked, mixed, or poorly defined (Sovner, 1986; Bouras, 1999).

Furthermore, people with more severe ID tend to express their psychic suffering through behavioural changes, including the increase of severity or frequency of PBs that could indicate the onset of a co-occurrent psychiatric disorder ('baseline exaggeration'; Sovner, 1986; Sturmey, 1990; Moss et al., 2000). In addiction, the symptomatology of psychiatric disorders in ID is often characterised by neurovegetative vulnerability; pains, organ dysfunction, and circadian rhythm disorders are frequently the main expression of emotional dysregulations (Costello & Bouras, 2006).

Atypical clinical presentation, including maladaptive behaviours, lent support for 'behavioural equivalent' substitutes of standard criteria. The evaluation is always based on direct observation of behaviours and the person's way of interacting with the outside world through the knowledge of precise meanings in the context of various environmental factors. However the majority of instruments that have been produced to date are only applicable to subjects with more mild cases of ID, have a suggestive value, are not very sensitive, or are time consuming (Bertelli et al., 2012).

Several studies highlighted the difficulties in applying diagnostic criteria for psychiatric disorders, designed to be used with the general population, to persons with ID. These criteria may be applied without adaptation only to borderline or mild ID level (Clarke et al., 1994), while they cannot be used with more severe ID (Sovner, 1986; Cooper & Bailey, 2001). The diagnostic criteria of the current nosographical systems, including the DSM-IV-TR, DSM-5, and ICD-10, show some characteristics that may interfere with the reliability of the psychiatric diagnosis in PwID. Many of the diagnostic criteria require verbal descriptions, especially of emotional state that are difficult to understand and express for PwID. Furthermore, the standard diagnostic criteria are not developed for use with an informant (e.g. caregiver, and family), and require detailed information on the psychopathology that not applicable to PwID. Finally, PBs have yet to be categorized in any of the nosographical systems (Cooper et al., 2003).

The Royal College of Psychiatrists (UK) and the National Association for Dual Diagnosis (USA) respectively have produced adaptations of the ICD-10 and DSM-IV-TR called Diagnostic Criteria for Learning Disability (DC-LD) (Royal College of Psychiatrists, 2001), and Diagnostic Manual - Intellectual Disability (DM-ID) (Fletcher et al., 2007). Additional consideration and researches have been conducted to produce a more reliable conversion in DC-LD 2. Furthermore, an update of the DM-ID for adaptation of the DSM-5 criteria is underway.

1.5.1.1 PSYCHIATRIC COMORBIDITY IN AUTISM AND AUTISM SPECTRUM DISORDER

Psychiatric comorbidities are common in ASD and frequently lead to further associated impairment. Diagnosis of co-occurrent psychiatric disorders is often challenging due to several difficulties including the core symptoms of ASD themselves, communication deficit, atypical presentation of psychiatric symptoms, and scarcity of standardised diagnostic tools (Chandrasekhar & Sikich, 2015). Furthermore, the clinical manifestations of ASD often overlap with the symptoms of other disorders;

thus, it can be difficult distinguishing between them (Matson & Sturmey, 2011; Underwood et al., 2010, 2015).

Mood Disorders

Depression, along with anxiety, is the most common disorder in adults with ASD (Royal College of Psychiatrists, 2014). The difficulty in detecting depression in this population is due to problems in communicating and expressing feelings of sadness, hopelessness, low self-esteem, guilt, or suicidal ideation (Stewart et al., 2006). Furthermore, individuals with ASD often show flat or constricted affect, so that changes associated with the onset of depression may not be identified (Chandrasekhar & Sikich, 2015). Depression in people with ASD is characterised by a variety of symptoms, including decreased interest in favourite interests, worsening in self-care capabilities, and decline in personal hygiene (Lainhart & Folstein, 1994; Charlot et al., 2008). In other cases, stereotyped and repetitive behaviours may intensify (Ghaziuddin et al., 2002), and there may be worsening of PBs such as agitation, aggression, or self-injury (Lainhart & Folstein, 1994; Gotham et al., 2015). Also, neurovegetative symptoms as changes in sleeping patterns, appetite, and weight are common, especially in those with lower verbal abilities (Chandrasekhar & Sikich, 2015).

Anxiety disorders

Clinical significant anxiety is common in individuals with ASD and is related to increased psychosocial, and familial impairment (Nadeau et al., 2011).

People with ASD and comorbid anxiety may show increased ritualistic behaviours and PBs (Davis et al., 2011). However, anxiety disorders can be difficult to diagnose in this group, due to difficulties in expressing worry and fear.

Study found that individuals with ASD, especially high-functioning, are likely to suffer from social anxiety, which may contribute to the avoidance of social interaction typically seen in this population this population. An important difference between social anxiety disorder and ASD is the presence in this latter group of social awkwardness. (Bejerot et al., 2014).

Obsessive-Compulsive Disorder

Obsessive thoughts and stereotypical behaviours are commonly observed in ASD and overlap with OCD in the symptomatic profile (Ivarsson & Melin, 2008). So it can be difficult to distinguish symptoms that are related to a comorbid OCD, particularly in people with lower functioning levels. However, studies have indicated that repetitive thoughts and autistic behaviours differ from those of the OCD (Ruzzano et al., 2015; Cadman et al., 2015). In OCD, typical obsessive themes include worries about germs, harm coming to self or others, distinguishing right from wrong, and guilt about morals, or religiosity. Therefore, typical compulsions include ritualized washing, checking, ordering, apologizing, or mental rituals such as counting or praying. Whereas people with ASD, may perform

repetitive or ritualistic behaviours such as ordering, arranging, counting, or touching/tapping (McDougle et al; 1995). However, people with ASD are not likely to think about their rituals and may present with limited insight into the reason behind their ritualized behaviours. People with ASD are also less likely to be using their ritualized behaviours to neutralize fear or anxiety as would be true for OCD. Rather, ritualized behaviours and repetitive thoughts may satisfy other needs, such as modifying sensory input, knowing what is going to happen next in their daily routine, controlling and gaining reinforcement from the environment, or preserving routine and sameness in their daily lives.

Psychotic disorders

Transition into adulthood and exposure to stressful events are related to the onset of brief psychotic episodes in adults with ASD. Furthermore, psychotic symptoms are often signs of an underlying mood disorder or a schizoaffective disorder (Underwood et al., 2015). The overlap between autism and SSD is the subject of this thesis and will be discussed in detail in a subsequent section.

Eating disorders

Eating disorders are often reported among adults with ASD, particularly pica, food refusal, and food selection for colour, type or texture. Selective food refusal is also associated with food spitting, obsessions, and rituals in ASD (Gravestock, 2000; Gravestock, 2003). Autism and eating disorders, especially anorexia nervosa, have common features concerning cognitive style and behaviours (Rastam, 2008), such as the tendency to focus on details and the insistence on sameness (Gillberg et al., 2007).

Post-Traumatic Stress Disorder

Although negative life events, physical and sexual abuse are quite common in people with ASD studies are lacking. Traumatic events and clinical presentation of PTSD are difficult to detect in people with ASD especially for their difficulties in defining their inner psychic state (Mehtar & Mukaddes, 2011). Diagnosis of PTSD require an accurate assessment to understand cognitive interpretation, PBs, emotional disorders, and recognise signs of increased physiological arousal and sensory processing of the traumatic events, which might otherwise be misdiagnosed as exacerbation of ASD symptoms.

1.5.1.2 PSYCHIATRIC COMORBIDITY IN INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

PwID can experience the full range of mental disorders, and there is evidence that occur more commonly than observed in the general population. The psychiatric diagnosis, already complex in the general population, becomes even more difficult in a person with ID, especially in the more severe

cases, where normal communication capacities are limited or absent. Psychiatric disorders are frequently underdiagnosed or misdiagnosed, and can markedly reduce cognitive and adaptive functioning.

Mood disorders

Depression is one of the most frequent psychiatric disorders in adults with ID. Research shows that PwID can suffer also from bipolar disorder, for which the incidence is higher than the general population. The main symptoms of mood disorders described in terms of observable behaviour include sadness, irritability, decreased social interaction, worsening of functioning levels, sleep disturbance, diurnal variation, and aggression (Hurley, 2008). Low appetite or other eating problems are two key signs in diagnosing depression, especially in people with more severe level of ID (Mayville et al., 2005), while understanding complex concepts such as guilt, thoughts of death or suicide are difficult.

Symptoms of mania include insomnia, increased activity, pressured speech, and psychomotor agitation (Vanstraelen & Tyrer, 2001; Matson et al., 2007). In addition to this usual presentation, atypical symptoms of mania are aggression and self-injurious behaviour (Hurley, 2008; Kendall & Owen, 2015).

Anxiety disorders

All types of anxiety disorders can occur in PwID. Clinical features of anxiety include fearful anticipation, irritability, concentration and memory problems, repetitive worrying thoughts, increased drinking, hyperventilation, increased urinary frequency, anger, sweating, avoidance behaviour, agitation, and excessive motor activity (Cooray & Bakala, 2005).

Studies found that PwID exhibit challenging behaviour such as aggression or self-injurious behaviour as a means of coping, especially in those with greater difficulty in communicating (Stavrakaki, 2002; Cooray & Bakala, 2005).

Psychotic disorders

The prevalence of psychotic symptoms in ID seems three times more frequent than in the general population (Ayub et al., 2015). Diagnosis of psychotic disorders is based on a complex assessment of subjective symptoms such as delusions and hallucinations. However PwID may exhibit strange behaviours to communicate unusual thoughts, especially in those with limited verbal skills.

An additional complicating issue is that many of the same behaviours that might indicate psychosis can also interpreted as features of ID. If a person with ID says that his name has been mentioned in the radio, or television, does not be misinterpreted as a delusion of reference. PwID may also think that someone is trying to control their own actions, because they require support of others. In grandiose delusions, the content can be quite simple in this population - for example, they might think they can drive a car.

It is important to distinguish true 'psychotic' symptoms from 'psychotic-like' symptoms; in the latter case 'fantasy thinking' can be part of the symptomatology of ASD. Furthermore, some adults with ID may speak to themselves, an object, or an imaginary person. These behaviours could be indirect signs of hallucinations, but could also be symptoms of ID caused by underlying brain abnormalities (Deb et al., 2001a).

Personality disorders

Features of borderline personality disorder, such as self-injurious behaviour, impulsive behaviours and affective liability, often occur in PwID (Mavromatis, 2000). However, communication deficit and maladaptive behaviours can make a personality disorder very difficult to diagnose in this population, especially in those with more severe impairment (Wilson, 2001; Alexander & Cooray, 2003). Also the diagnostic criteria of dependent and anxious/avoidant personality disorders may be difficult to identify in this group (Alexander & Cooray, 2003).

Eating Disorders

Numerous and heterogeneous types of eating and feeding problems affect PwID (Gal, 2011). Common dysfunctions are pica (Hove, 2004), rumination/regurgitation, psychogenic vomiting (Gravestock, 2000), food faddiness, and selective food refusal (Gravestock, 2000; Royal College of Psychiatrists, 2001).

Post Traumatic Stress Disorder

PwID have been found to more likely to experience traumatic events, such as sexual and physical abuse (Focht-New et al., 2008). Fewer abilities in managing adverse life events, maladaptive coping strategies, and low social support make PwID more vulnerable to develop PTSD (Tomasulo & Razza, 2007). Language deficit and impairment in identification or description of his experiences and emotional state make it difficult to identify PTSD in individuals with ID (Hall et al., 2014). Studies found that traumatic experience in this population often manifests itself in disorganized or agitated behaviour, while re-experiencing the trauma takes the form of behavioural acting out of traumatic experiences, self-injurious behaviour, nightmares without recognizable trauma-specific content that can appear as symptoms of psychosis (Fletcher et al., 2007; Mevissen & de Jongh, 2010).

1.5.1.3 PSYCHIATRIC COMORBIDITY IN SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS

Individuals with SSD show high rates of psychiatric comorbidity including anxiety, depression, OCD, and especially substance abuse (Buckley et al., 2009; 2015).

Depression

Depression can be difficult to identify in people with schizophrenia, because some negative symptoms such as anhedonia, abulia, alogia, amotivational state, avolition, and asociality can mimic depression features (Mulholland & Cooper, 2000). Study found that depressive symptoms in SSD are related to feelings of loss, distress and hopelessness (Bosanac & Castle, 2012).

Depressive symptoms can occur throughout all phases of the illness, during the course of the disorder, in the post-psychotic interval, and may be also associated with the prodromal symptoms (Buckley et al., 2009). The post-psychotic depression is considered a psychological reaction to the episode that occurs only during the residual phase of schizophrenia.

Research finding showed that depression in people with schizophrenia is associated with a poorer clinical outcome, including more psychotic relapses, suicidality and reduced quality of life (Sim et al., 2004; Buckley et al., 2009; Tsai & Rosenheckc, 2013).

Anxiety symptoms and anxiety disorders

Anxiety symptoms are frequently observed among patients with schizophrenia and commonly occur along with other mental disorders. Anxiety may appear both spontaneously, in response to psychotic symptoms, and as common side effect of antipsychotic drug (Tibbo et al., 2003). People who suffer from severe anxiety seem to also have a significant vulnerability to substance use and also to suicidal ideations or suicidal behaviours (Fialko et al., 2006).

Considering specific types of anxiety disorder, panic symptoms and panic attacks seem more common in people with paranoid ideation, and can present as part of the prodromal picture of psychosis (Labbate et al., 1999; Baylé et al., 2001). Social anxiety is a frequent but often unrecognized comorbid disorder in schizophrenia, and is associated with poor outcome (Pallanti et al., 2004).

Obsessive Compulsive Disorder

Comorbidity with OCD symptoms is commonly reported in those with schizophrenia. OCD can occur both in the context of disorder, associated with the prodromal symptoms and in the post-psychotic state during the course of chronic schizophrenia (Goodwin et al., 2003; Schirmbeck & Zink, 2013). OCD can be difficult to identify because the symptom of schizophrenia might overlap with the OC features, especially in cases of catatonic schizophrenia (Fink & Taylor, 2001; Fink, 2013).

Study found that the most prevalent symptoms in people with schizophrenia and comorbid OCD were aggressive and contamination obsessions, followed by somatic and sexual obsessions; the most prevalent compulsions were cleaning and washing (Poyurovsky et al., 2003). The existence of a comorbid OCD is related to positive symptoms and especially to compulsions, that seem to be a phenomenon which is less delusion dependent (Eisen et al., 1997; Öngür & Goff, 2005).

Post Traumatic Stress Disorder

Traumatic events often occur in people with schizophrenia, especially in childhood. In the latter case trauma is a risk factor for the onset of psychosis (Morgan & Fisher, 2006; Buckley et al., 2009). Schizophrenic patients are more likely to experience trauma than the general population due to illness-related features, environmental factors, and comorbid substance use (Picken & Tarrier, 2011).

PTSD seems to have a clear link with positive symptoms; studies found that PTSD comorbid with schizophrenia is most commonly associated with paranoia, and higher severity of delusions and hallucination (Resnick et al., 2003; Gearon et al., 2004).

It is less clear whether the symptoms of PTSD are associated with increased (Duke et al., 2010) or decreased negative symptoms (Read et al., 2003; Strauss et al., 2009).

Other researches found that PTSD in schizophrenia is associated with more severe psychopathology rather than with cognitive impairment and functional deterioration (Duke et al., 2010; Peleikis et al., 2013).

Substance abuse

Alcohol and other drugs abuse are the most prevalent co-occurring disorders in people with schizophrenia. Caffeine, cannabis, alcohol, cocaine and especially tobacco, are the substance most commonly abused by this population (Winklbaur et al., 2006; Thoma & Daum, 2013).

Substances producing sedative and relaxing effects are often used to self-medicate the symptoms of anxiety, while abuse stimulants to self-medicate negative symptoms. The self-therapeutic hypothesis suggests that smoking may improve attention and memory deficits often observed in those with SSD (Rezvani & Levin, 2001).

Alcohol and substance use disorders are related to worse clinical outcomes, increased positive symptoms, higher rate of psychosis relapse, physical illnesses, and other mental health disorders (Krystal et al., 2006; Winklbaur et al., 2006; Buckley et al., 2009). In particular, cannabis abuse may trigger psychotic relapse and is associated with poorer treatment compliance (Volkow, 2009).

1.5.2 PREVALENCE OF COMORBID PSYCHIATRIC DISORDERS

1.5.2.1 PREVALENCE OF PSYCHIATRIC DISORDERS IN AUTISM AND AUTISM SPECTRUM DISORDER

The prevalence rate of psychiatric disorders in adults with ASD ranges from 16% to 35% (Royal College of Psychiatrists, 2014). The prevalence of depression and anxiety in adults with ASD is estimated between 15%-42% and 7%-22%, respectively (Ghaziuddin et al., 2002; Matson & Cervantes, 2014). OCD prevalence rates ranged from 7% to 24%, and psychotic symptoms from 12% to 17% (Leyfer et al., 2006; Royal College of Psychiatrists, 2014). In people with ASD, the rate of exposure to trauma in childhood is estimated between 25% and 45% (Costello & Angold, 2000;

McCloskey & Walker, 2000), while the risk of developing a PTSD after trauma ranged from 5% to 45% (McCloskey & Walker, 2000). The lifetime prevalence rate of PTSD in this population is estimated between 6–8% (Stallard, 2006).

1.5.2.2 PREVALENCE OF PSYCHIATRIC DISORDERS IN INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

ID is associated with a high rate of psychiatric disorders; the point prevalence is about 40% and the annual incidence 8% (Cooper et al., 2007c). Cooper and her colleagues highlight how psychiatric comorbidity may vary considerably depending on the diagnostic criteria applied, ranging from 52.2% when the diagnosis is based only on clinical assessment, to 45.1% when the diagnosis is based on the DC-LD, up to 11.4% in surveys applying the criteria of the DSM-IV-TR, or even up to 10.9% by application of the Diagnostic Criteria for Research of the ICD-10 (DCR-ICD-10; WHO, 1993).

The prevalence of unipolar depression in PwID is estimated about 3.8%, bipolar disorder 1.3%, and manic episode 0.6% (Cooper et al. 2007b,c; Morgan et al., 2008). The rate of anxiety disorders is approximately 3.2% using DC-LD criteria. Point prevalence of generalised anxiety disorder was 1.7%, and of agoraphobia and panic disorders about 0.4% and 0.2%, respectively (Reid et al., 2011). The prevalence rate of psychotic disorders in adults with ID ranges from 2.6% to 4.4% depending upon the diagnostic criteria used (Cooper et al., 2007a,c). Problems with eating have been estimated to prevail in about one third of PwID (Matson & Kuhn, 2001; Gal et al., 2011), and up to 80% in people with more severe impairment and PBs (Gal et al., 2011; Matson & Kuhn, 2001). Prevalence rates of PTSD vary substantially, from 2.5 to 60 % (Mevissen & de Jongh, 2011). Rates of co-occurring personality disorder ranges from 1% to 91% in a community setting and from 22% to 92% in hospital settings (Alexander & Cooray, 2003); Wieland and colleagues (2013) found that personality disorder-NOS (19.1%) was most common, followed by borderline personality disorder (8.7%).

1.5.2.3 PREVALENCE OF PSYCHIATRIC DISORDERS IN SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS

The prevalence rate of depression in people with schizophrenia ranges from 23% to 57% (Buckley et al., 2009, 2015). More than 65 % of patients with schizophrenia show symptoms of anxiety (Temmingh & Stein, 2015), with a prevalence of 9.8% (4.3%–15.4%) for panic disorders, 10.9% (2.9%–18.8%) for generalised anxiety disorder, 12.4% (4.0%–20.8%) for PTSD, and 14.9% (8.1%–21.8%) for social phobia. The prevalence of OCD also varies widely across the studies with a rate ranging from 7.0% to 17.1% (Achim et al., 2011; Swets et al., 2014). The prevalence rate of substance abuse is particularly high among people with schizophrenia. It is estimated that more than 47% of patients show alcohol or substance abuse, and more than 70% are nicotine-dependent (Brady & Sinha, 2005).

1.5.3 ETIOPATHOGENESIS OF COMORBID PSYCHIATRIC DISORDERS

1.5.3.1 ETIOPATHOGENESIS OF PSYCHIATRIC DISORDERS IN AUTISM AND AUTISM SPECTRUM DISORDER

Little is known about the causes of comorbid psychiatric disorders in ASD (Ruedrich, 2010). Specific risk factors for psychiatric disorders across the lifespan include level of functioning, age, family history, genetic factors, and coping strategies (Helvershou et al., 2011; Chandrasekhar & Sikich, 2015). Significant negative life events, such as family sickness and bereavement, changes in caregivers, structure or daily routine may significantly contribute to the occurrence of psychiatric disorders in ASD (Ghaziuddin et al., 1995, 2002). People with ASD with higher awareness of their low social impairment, more self-perceived impairment and higher rates of anxiety and rumination may show lower self-esteem, and discouragement that seem to increase the risk of developing or triggering depression (Sterling et al., 2008; Hofvander et al., 2009; Buck et al., 2014).

1.5.3.2 ETIOPHATOGENESIS OF PSYCHIATRIC COMORBIDITY IN INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

As well as having all the risk factors that are relevant for the whole population, PwID may have extra risk factors (Smiley et al., 2007). In some cases the comorbid psychiatric disorders in ID are sequelae of other neurological, metabolic, and infective causes of ID; in others, the risk factors for psychiatric disorders are not the same that underlying the condition of ID.

The vulnerability to psychiatric disorders is created through the interaction of biological, psychological, social, and developmental factors including sensory impairments, multiple prescribed medications, multiple life events, traumatic experiences, limited communication skills, low self-esteem, and limited coping strategies, as well as genetic and organic factors such as thyroid problems and epilepsy (Deb et al., 2001b; Luckasson et al., 2002; Cooper et al., 2007c).

1.5.3.3 ETIOPHATOGENESIS OF PSYCHIATRIC COMORBIDITY IN SCHIZOPHRENIA AND SCHIZOPHRENIA SPECTRUM DISORDERS

Schizophrenic patients may develop comorbid psychiatric disorders both by chance, consequently to the core symptoms, and as a consequence of some underlying shared liability with schizophrenia (Buckley et al., 2009). Overlap in symptoms, genetic linkage, neurobiology and neurotransmission suggests a common etiological mechanism that underlies the comorbid psychiatric disorders and schizophrenia (Samson & Wong, 2015). Dopamine and serotonin deregulation are neurotransmitter systems involved in schizophrenia, as well as in depression and OCD.

Furthermore there is a growing evidence of neurochemical shared factors of vulnerability between substance abuse and schizophrenia (Bottas et al., 2005; Moore et al., 2007; Buckley et al., 2009). Also psychotic symptoms or negative life experiences may themselves be considered as stress factors

associated with co-occurring psychiatric disorders including PTSD (Shaw et al., 2002). In addition, there is some evidence that pharmacological treatments might directly aggravate psychiatric symptoms (Harrow et al., 1994; Green et al., 2003).

1.5.4 CONTINUITY, OVERLAPPING AND CO-OCCURRENCE BETWEEN INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND SCHIZOPHRENIA SPECTRUM DISORDERS

Both ID and ASD are metasyndromic groups including several and different clinical conditions (Salvador-Carulla & Bertelli, 2008). The difficulties in defining the diagnostic boundaries between ASD and ID are largely documented (Palucka et al., 2008; Bryson et al., 2008; Bradley et al., 2011b). Some studies report that a 30 – 40% of PwID present also pervasive autistic traits (Morgan et al., 2002; La Malfa et al., 2004; Cooper et al., 2007c), whereas a 70% of patients with autism are also affected by ID (Bryson & Smith, 1998; Baird et al., 2006; U.S. Developmental Disabilities Monitoring Network Surveillance, 2006; Edelson, 2006; Matson & Shoemaker, 2009; Hoekstra et al., 2009; Noterdaeme & Wriedt, 2010). The boundaries between ID, ASD and SSD are also more difficult to define, and they constitute an important issue considering the high co-occurrence of Schizophrenia and ASD (Stahlberg et al., 2004; Mouridsen et al., 2008), especially in PwID (Ghaziuddin, 2005; Cooper et al., 2007c). Such complexity has been associated to their broad phenotypes that overlap over the spectra (King & Lord, 2011), the similar cognitive dysfunctions (Kerns et al., 2008; Sasson et al., 2011), alterations of brain regions (Toal et al., 2009), dysregulated neurotransmission (Murphy et al., 2006; Tarabeux et al., 2011) and shared genetic factors (Burbach & van der Zwaag, 2009; Carroll & Owen, 2009; Pinto et al., 2010).

Interestingly, both autism and schizophrenia have been described as common sense disorders (Minkowski, 1927; Stanghellini, 2000). Specifically, Minkowsky made a distinction between ‘autisme riche’ and ‘autisme pauvre’, indicating with the former an intensive attempt to find meanings in the environment that is also peculiar of what is defined as productive schizophrenia; whereas the latter refers to a prevalent lack of contacts with the external world and that is closest to the current concept of autism.

There is evidence of the higher rate of psychotic disorders in adult with ID in respect with the general population, with some studies reporting a rate of 3% for schizophrenia in PwID in comparison to the 1% in people without ID (Turner, 1989; Hassiotis et al., 2001; Cooper et al., 2007c), and others suggested a comorbid SSD in 4.4% of PwID (Cooper et al., 2007c).

However, in a context of a dual diagnosis (i.e., a developmental disorder such as ASD or ID and psychiatric disorder) there is evidence of a general tendency to underestimate ASD in PwID in presence of a diagnosis of schizophrenia (Savage et al., 2007; Palucka et al., 2009; Bradley et al., 2011b). Research showed that about 40% of the items which examined a potential psychosis obtained a high score in presence of autism (Helverschou et al., 2008). Interestingly, in a twenty year follow up study, authors found that in twenty adults who received as children a diagnosis of ‘childhood schizophrenia’ (infantile autism) their symptoms did not changed over time (Howells & Guirguis, 1984). Moreover, although none of them met Schneider’s criteria for schizophrenia (i.e., ‘first rank’

symptoms), they all met Feighner's criteria for schizophrenia (Feighner, 1972), which coincide with Kraepelin's dementia praecox, Crow's type II schizophrenia (defect state) and DSM III residual schizophrenia (Howells & Guirguis, 1984).

Data collected from a survey conducted by the National Institute of Mental Health (2004) on a sample of subjects with childhood-onset schizophrenia found that a 21% of participants presented a lifetime diagnosis of ASD-NOS (Sporn et al., 2004; Towbin, 2005) and some authors found that a 26% of adults psychiatric patients had undiagnosed ASD and received instead a diagnosis of schizophrenia (Nylander & Gillberg, 2001). It has been also described a subset of patients affected by a complex neurodevelopmental disorder characterized by impairments crossing the diagnostic categories, that received the name of 'autism-plus' disorder (Cochran et al., 2013)

It is important to note that the complex diagnosis in people with ASD and ID is essential also in areas where there are concerns about mental ill-health and the management of psychiatric comorbidity.

It is well known that individuals with ID are at greater risk of hospitalization for behavioural and mental distress, and this has been associated to the difficulties in recognizing co-occurrent ASD or other psychiatric disorders (Lunsky et al., 2009). Problem behaviours (PBs) and autism have been found as the strongest predictors of hospital admission (Cowley et al., 2005; Bhaumik et al., 2008), and they resulted frequently associated with mood disorders and aggressive behaviours (Palucka & Lunsky, 2007).

Therefore, there is a considerable amount of data confirming the extreme complexity in the detection of psychiatric illness because of the problematic distinction of psychiatric symptoms from the autism core symptoms and ID (Lainhart, 1999; Reaven & Hepburn, 2003; Ghaziuddin, 2005).

It is now clear that the assessment of mental health problems in individuals with ID and ASD raises several theoretical questions and methodological dilemmas, and this is due to the definition and classification of mental health problems and to the nature of psychiatric assessment (Smiley, 2005; Costello & Bouras, 2006), in consideration that the mental illness presentation in PwID and ASD is often atypical (Bradley et al., 2011b).

Data from literature showed that mood disorders (Bradley & Bolton, 2006), anxiety disorders (Hutton et al., 2008), SSD, and impulse control disorders (Bradley et al., 2004, Gadow et al., 2005; Hill and Furniss, 2006; McCarthy, 2007) are the most frequent psychiatric conditions in people with ASD and ID, and teens with autism and ID seem to present increased rates of inattention, hyperactivity and impulsivity compared with people affected by ID alone (Bradley & Issacs, 2006). Moreover, people with both autism and ID resulted more vulnerable to anxiety, mood, sleep problems, organic syndrome, stereotypies and tics (Bradley et al., 2004).

In this scenario, the investigation of behavioural phenotypes may help to understand mental ill-health in some developmental conditions. For example, genetic studies found a statistically significant comorbidity between Fragile X Syndrome (FXS) and ASD, with a prevalence rate ranging from 7 to 25% (Levitas et al., 1983; Hagerman et al., 1986; Bregman et al., 1987; Bailey et al., 1998). However,

neither the particular psychiatric features of FXS nor correlations with age or genetics have been investigated. The increased occurrence of psychiatric disorder in individuals with FXS has been confirmed also by the research group of the Weinberg Centre for Child Development at Tel Hashomer in Israel (Gabis et al., 2011). Indeed, findings showed an occurrence of specific phobias and vocal tics in about half of participants, whereas the criteria for autistic symptoms and schizoid personality were met by one third of them.

It is evident how a more accurate assessment process of both ASD and ID could provide a better understanding of the 'psychiatric' presentation and of the associated mental distress (Bradley & Bolton, 2006; Palucka et al., 2008; Bradley et al., 2011a,b).

1.6 CATEGORICAL AND DIMENSIONAL APPROACHES

The DSM-5 introduces an integration of a dimensional approach to diagnosis and classification with the DSM-IV-TR categorical approach (APA, 2013).

Previous editions of DSM used a categorical model requiring a clinician to determine that a disorder was present or absent. The dimensional approach allows a clinician more liberty to assess the severity of a condition and does not imply a real threshold from low-functioning forms to forms with very high general skills. All the psychiatric disorders in DSM-5 remain in specific categories, while measures indicating degree of severity have been added to several combined diagnoses. Indeed, the DSM-5 combines four different categorical disorders in the ASD diagnosis, and conceptualizes them as occurring along a single spectrum characterized by dysfunctional social communication and restricted, repetitive behaviours or interests. Using DSM-IV, people with such symptoms could be diagnosed with four separate disorders: autistic disorder, Asperger's disorder, childhood disintegrative disorder, or PDD-NOS.

Given the phenotypic heterogeneity of this condition, the DSM-5 introduced the concept of neurodevelopmental disorders that include a range of disorders associated with learning difficulties, skills impairment, high reduction in logical-deductive intelligence, and significant difficulty in sharing emotional content (APA, 2013).

Each of the two classificatory approaches has advantages and disadvantages. Categorical approach is based on the kraepelinian and neo-kraepelinian perspective and refers to the process of dividing mental disorders into discrete entities, whereas the dimensional concept of spectrum, often used interchangeably to that of the continuum, includes a set of clinical forms which show a similar appearance or are thought to be caused by the same underlying etiological mechanism, differentiated according to increasing severity. The principal disadvantage of the categorical model is its tendency to encourage a 'discrete entity' view of the psychiatric disorders. Conversely, dimensional approach introduces quantitative variation and graded transition between different forms of the disorder, as well as between normality and pathology (Maj et al., 2002; Jablensky & Kendell, 2002).

Since 2009, a dimensional approach to neural circuits and their connections with psychopathology was promoted. The National Institute of Mental Health (NIMH) instituted the Research Domain Criteria (RDoC) project to develop a research classification system for psychopathology based on neurobiology and observable behaviour.

The RDoC is based on three assumptions. First, the RDoC framework conceptualizes the mental illnesses as disorders of brain. While neurological disorders show identifiable lesions, mental disorders were considered as disorders of brain circuits. Second, RDoC assumes that the dysfunction in neural circuits can be detected by some screening and diagnostic tools employed in neuroscience, such as the fMRI. Third, the RDoC framework assumes that data from genetics research and clinical neuroscience data from genetics and clinical neuroscience will yield biosignatures that will augment clinical symptoms and signs for clinical management. RDoC is intended to support research toward a

new classification that encourages investigators to approach to the study of the genetic, neural, and behavioural features of mental disorders (Insel et al., 2010; Cuthbert & Insel, 2013; Insel, 2014).

In this context, advances in knowledge of early brain development brain highlighted the role of the neurodevelopmental perspective in theorizing about the aetiology of disorders. Distinctive types of psychopathology may have early onset, features in common, and different time courses in symptoms depending on the variations of the same underlying disposition.

Genetic, anatomical, and functional imaging studies in ASD found an atypical organization of subcortical and cortical areas related to autistic symptoms. A damage occurring early in the brain development may induce a cascade of more complex deficits. Furthermore, neuronal circuits interact with others across the different brain regions. The cumulative consequences of these interactions among complex biological and also environmental systems alter the course of brain development.

Advances in the development of dimensional models and approaches to research on psychopathology found that behavioural, cognitive, social, and emotional competencies share neurobiological bases, evolve across the brain development, and vary across individuals in different traits, abilities or mental disorders (Casey et al., 2014).

Research in ASD and others neurodevelopmental disorders is in progress. How damage in one system may lead to deficit in another or how different brain regions develop and interact with others remains largely unknown.

According to RDoC framework, in this study we have indirectly investigated the brain mechanisms associated with ID, ASD, and SSD.

Disruptions in specific cerebro-cerebellar circuits in ASD might interfere with the specialization of cortical regions involved in motor control, memory, attention, language, and social interaction, leading to deficit in these domains. Extensive connections within the brain provide an anatomical substrate for the broad range of clinical presentations of ASD and others neurodevelopmental disorders (D'Mello & Stoodley, 2015).

The international scientific community considered the extreme variability of symptoms as a polymorphism due to a complexity of different causal factors, both biological, and environmental. Among the biological factors, genetic type has a predominant role. A recent review conducted by Torres and colleagues (2015) found that CNVs of 1q21.1, 3q29, 15q11.2, 15q13.3, 16p11.2, 16p13.1 and 22q11 chromosomal regions result in a wide phenotypic spectrum, ranging from normal development to learning problems, including ID, ASD and SSD. Waltereit and collaborators (2013) also analysed the functions of genes mutated in these three disorders, and selected some shared mechanisms in neurodevelopmental pathways, finding some similarities.

Emerging evidence suggest that ID, ASD, and also SSD, are part of a single group of neurodevelopmental disorders. Aetiologically all the three syndromes are considered to result from the overlap between different combination of specific causative factors both genetic and environmental

that influence brain growth and maturation with subsequent effects on general and specific impairments of cognitive functioning (Owen et al., 2011).

1.7 DIFFERENTIAL DIAGNOSIS BETWEEN INTELLECTUAL DISABILITY, AUTISM SPECTRUM DISORDER AND SCHIZOPHRENIA SPECTRUM DISORDERS

1.7.1 CLINICAL PRESENTATION

A reliable diagnosis requires a great knowledge of target symptoms and a considerable attention to the details of differential diagnosis. Basically, ID is characterized by significant impairments in cognition, social and adaptive behaviour (Matson et al., 2005; Downs et al., 2008; Lifshitz et al., 2008; Myrbakk & von Tetzchner, 2008a; Thirion-Marissiaux & Nader-Gosbois, 2008; Yalon-Chamovitz & Weiss, 2008; Zayac & Johnston, 2008), and by the frequent presence of stereotypies, challenging behaviours and autistic symptoms (Lee et al., 2008; Wilkins & Matson, 2009).

The core symptomatology characterizing ASD consists of impairments in social interaction (e.g., inadequate eye contact, inappropriate peer relationships, lack of emotional reciprocity), impaired verbal and non-verbal communication (e.g., language delay, poor conversation skills, inability to play imaginatively), and a pattern of repetitive behaviours and restricted interests (e.g., repetitive motor movements, intense attraction to particular objects or parts of objects) (Matson et al., 2009a,b; Briegel et al., 2009; Gillberg, 2010; Horovitz & Matson, 2010; Leung et al., 2010; Smith & Matson, 2010a,b,c). However, some of these difficulties are also found in PwID (Lee et al., 2008; Matson & Shoemaker, 2009).

As mentioned before, there is an increased risk to receive a diagnosis of schizophrenia spectrum and other psychotic disorders in this kind of population, and there is evidence showing that a first diagnosis of schizophrenia or psychosis tends to be confirmed over time (Nylander & Gillberg, 2001; Bryson et al., 2008; Palucka et al., 2008; Bradley et al., 2011b).

In order to provide a reliable and robust diagnosis of psychotic disorder in PwID, It is of extreme relevance the evaluation of the impact that the ID itself (e.g. cognitive fragmentation associated with stressful life events) and a possible co-existing ASD exert on the individual's clinical presentation (Loos & Loss, 2004; Shah & Wing, 2006; Bradley et al., 2011b), even with the consideration of the context in which the psychotic-like symptoms appear (Hubert & Hollins, 2006).

It is important to emphasize that some psychotic-like behaviour such as talking to one's self, regression, as well particular postures that may be assumed in response to stressful events, can be part of the ID symptomatology, also without ASD (O'Dwyer, 2000; Hurley et al., 2003). Even some particular ways of experiencing the world in ASD that may result in a specific symptomatology, such as bizarre expression or fantastic thinking, may be confused with psychotic symptoms (Palucka et al., 2009).

In this challenging situation, the careful evaluation of the individual's developmental history, the prodromes, the onset and the course of the condition, the presence of positive symptoms has a central role for determining whether the clinical manifestations belong to the autistic or schizophrenic spectra, or are the result of their comorbidity (Roy & Balaratnasingam, 2010; Paula-Pérez, 2012).

Data documenting neurological and social development from infancy are of great value, in consideration that the abnormalities in social cognition typically present in ASD can be detected in the first year of age; conversely, in schizophrenia they are evident at seven-eight years old, and more frequently in teenage years.

In terms of differential diagnosis, it has been reported that SSD and ASD can be distinguished by the interest towards others (Fitzgerald, 2014), the level of understanding others' meaning and emotions, the manifestation of positive symptoms, and the deficits in global cognition. As Crespi and Badcock (2008) reported, individuals with ASD are characterized by an unusual disinterest in shared sense and others' thought, whereas those with schizophrenia try to interpret the other's thought and intentions, and such effort in understanding can become even an obsession. Furthermore, evidence shows that people with ASD generally lack of contact with other persons from the infancy, and usually this can be evident in the first years of life; conversely, a progressive loss of contact appears to characterize individuals affected by schizophrenia (Asperger, 1944).

According to literature, social cognition refers to a number of abilities encompassing the detection of biological motion, the identification of facial affect and metacognitive skills such as the theory of mind and the attribution of mental states (Blake et al., 2003). The impairments in social cognition characterizing people with ASD adversely affect face processing, emotion recognition, eye gaze processing, face scanning processing, biological motion perception, dynamic social interactions, and interpretation of emotionally charged situations (Klin et al., 1999; Baron-Cohen et al., 1999; Edwards et al., 2002; Klin et al., 2002; Pelphrey et al., 2002; Blake et al., 2003; Sasson, 2006; Sasson et al., 2007). It is noteworthy that similar deficits, e.g. impaired perception of emotions, theory of mind, perception of social cues, complex social judgments, face scanning processing, and biological motion have been also reported in people with schizophrenia (Loughland et al., 2002; Kim et al., 2005; Bora et al., 2009; Van't Wout et al., 2009; Haut & MacDonald, 2010; Kohler et al., 2010).

However, there is evidence that these two conditions can be differentiated considering the strategies that people affected use for evaluating events characterized by social and emotional contents. In fact, in individuals with schizophrenia it has been described the so-called "jumping to conclusions" bias, when they have to evaluate emotional information (Freeman, 2007); instead, in people with ASD a poor perceptual integration has been considered the cause of a dysfunctional decoding strategy (Happé & Frith, 2006). Consequently, it has been elaborated a new theory conceptualizing ASD as an hyposocial disorder and schizophrenia as the opposite, because it is characterized by an hyper, even though dysfunctional, development of social attitude (Crespi & Badcock, 2008; Crespi et al., 2010).

In contrast with what is usually described regarding ASD, in ID social cognition appear less compromised in respect to the general intellectual capacity, and this pattern tends to remain stable during the lifespan. On the other hand, impairments in cognitive and social abilities that characterize schizophrenia appear to gradually increase over time, and may present an exacerbation in early adulthood after the first psychotic episode (Pinkham et al., 2007). In addition, delusions and

hallucinations are typical symptoms of schizophrenia and generally are not present in ID as well in ASD (Bradley et al., 2011b). Nevertheless, approximately 90% of children with autism have abnormalities in sensory perception affecting smell, taste and also vision (Leekam et al., 2007), and they can be mistaken for hallucinations. Also the presence of pretend/imaginary friends, relationships with a 'transitional object' (when a toy is treated as a real friend), stereotypic preoccupations, concrete externalization of thoughts or conscience and pseudo-hallucinations should not be confused with hallucinations and delusions (Dossetor, 2007). Other features that can help to differentiate autism and schizophrenia are the typical lack of flexibility and the disturbance in response to routine changes characterizing autism (Fitzgerald, 2014), and the bizarre behaviour including stereotypical speech, echolalia, posturing, grimacing, and rigidity characterizing the catatonia spectrum. However, mild forms of catatonia may also occur in autism, since they have been observed in approximately 17% of adolescents and young adults affected (Wing & Shah, 2006).

In consideration of the current classification systems, it is very likely that the disorganized subtype of schizophrenia can be confused with autism, because of its core symptomatology represented by disorganized speech and behaviours, and flattened affect. This can be also the case for the residual type, because of the persisting negative symptoms after the psychotic episode (Roy & Balaratnasingam, 2010).

It is possible to observe a mixed form of catatonia, autism and psychosis, when none of the single diagnoses could explain better the clinical presentation. If a single diagnosis is given, such as 'schizophrenia', the standard pharmacological interventions usually do not produce the expected response (Shorter & Wachtel, 2013).

A recent study revealed the presence of a relationship between autistic symptomatology and schizotypal traits, and interestingly autism symptoms resulted associated with negative, disorganized and positive schizotypal ones (Ford & Crewther, 2014). It is noteworthy that individuals with an ASD diagnosis present some schizophrenia spectrum traits during the years of adolescence, and such overlap includes not only the negative schizotypal symptomatology, but also the disorganized and positive symptoms (Barneveld et al., 2011).

1.7.2 PSYCHIATRIC COMORBIDITY

As Boucher et al. (2008) reported, people with both ID and ASD present several core symptoms and deficits which are not seen in ID and ASD alone, and a different frequency of comorbid disorders. Research showed an inverse relationship between IQ and severity of ASD, and the lower the IQ and the higher the rate of challenging behaviours in ASD (O'Brien & Pearson, 2004; Murphy et al., 2009). Conversely, the severity level of ASD symptoms - and not that of ID - resulted directly associated with the rates of stereotypies (Goldmon et al., 2009; Matson & Kozlowski, 2011).

Accumulated evidence show the relevant impact that a comorbid condition can have on a person's life. It has been reported the greater risk of hospitalization for individuals with ID for behavioural and

mental distress caused by a not recognized ASD or other comorbid conditions (Lunsky et al., 2009), and some studies demonstrate that PBs and autism are the strongest predictors of hospital admission for PwID (Bhaumik et al., 2008; Cowley et al., 2005). Moreover, they appear frequently associated with mood disorders and aggressive behaviours (Palucka & Lunsky, 2007).

It is extremely complex to identify the presence of psychiatric disorders in individuals with autism and ID, because of problems in separating psychiatric manifestations from the autism and ID core symptomatology (Lainhart, 1999; Reaven & Hepburn, 2003; Ghaziuddin, 2005).

For this and other reasons, the diagnostic assessment of mental health problems in individuals with ID and ASD raises still concerns. At the centre of debate there are the definition and classification of mental health conditions, and the nature of psychiatric assessment (Smiley, 2005; Costello & Bouras, 2006), in consideration of the largely known atypical presentation of mental illness in PwID and ASD (Bradley et al., 2011b).

Among comorbidities, mood disorders (Bradley & Bolton, 2006), anxiety disorders (Hutton et al., 2008), SSD, and impulse control disorders (Bradley et al., 2004, Gadow et al., 2005; Hill & Furniss, 2006; McCarthy, 2007c) have been described as the most frequent psychiatric conditions in people with ASD and ID, and higher rates of inattention, hyperactivity, and impulsive behaviours have been observed in teens with both autism and ID in comparison with those without ASD (Bradley & Issacs, 2006). In addition, people with both conditions appear more vulnerable to anxiety, mood, sleep problems, organic syndrome, stereotypies and tics (Bradley et al., 2004).

The study of behavioural phenotypes may be extremely useful to promote further knowledge about some developmental conditions such as Fragile X Syndrome (FXS), in which genetic studies showed a prevalence of comorbid ASD ranging from 7 to 25% (Levitas et al., 1983; Hagerman et al., 1986; Bregman et al., 1987; Bailey et al., 1998). Data relative to the peculiar psychiatric characteristics of FXS and genetic constitution are still lacking, however a recent study performed by the research group of the Weinberg Centre for Child Development at Tel Hashomer in Israel (Gabis et al., 2011) confirmed the frequent occurrence of psychiatric disorders in people with FXS. In such study, specific phobias and vocal tics were present in about half of participants, and interestingly one third of them met the criteria for autism and schizoid personality.

1.7.3 NEUROANATOMICAL FEATURES

There is consistent evidence suggesting some neuroanatomical alterations in people with ASD. As mentioned above, specifically, increased gray matter volume have been observed bilaterally in the cerebellum, in the middle temporal gyrus, in the right anterior cingulate cortex, caudate head, insula, fusiform gyrus, precuneus and posterior cingulate cortex, and in the left lingual gyrus. On the contrary, there is evidence of reduced gray matter bilaterally in the cerebellar tonsil and inferior parietal lobule, in the right amygdala, insula, middle temporal gyrus, caudate tail and precuneus, and in the left precentral gyrus. As would be expected on the basis of the clinical heterogeneity of the disorder, ASD

is not associated with abnormalities in one specific location alone, but it seems to result from alterations in multiple, spatially distributed, neural systems. Findings from neuroanatomical studies show that anomalies are prevalent in the neuroanatomical networks, including the limbic system, frontostriatal system, frontotemporal and frontoparietal network, as well as the cerebellar system. It is likely that the distinct clinical phenotypes partially reflect the different patterns of increased/decreased brain volume (Cauda et al., 2011). Neuroimaging studies found a reduction in number and size of neurons in the fusiform gyrus (FG), a widening and an activation deficit of the superior temporal sulcus (STS), and a decrease in the pruning within the amygdala (AMY) in ASD (Howard et al., 2000; van Kooten et al., 2008; Jou et al., 2010).

Although the recognition of impairments in social cognition also in schizophrenic patients, there are only a few studies investigating FG, AMY, and ventrolateral prefrontal cortex functionality, and that highlighted levels of hypoactivation comparable to those found in ASD (Pinkham et al., 2008). It is reasonable to assume that the limbic system, and in particular the AMY altered functioning, has not the same central role in the pathophysiology of social cognition in schizophrenia which instead has in ASD. Interestingly, however, other abnormalities in the fronto-limbic circuitry in response to social emotional cues have been described in schizophrenia, such as reduced frontal cortex volumes (Convit et al., 2001), and a decreased activation in the medial-prefrontal cortex during theory of mind tasks (Brunet et al., 2003). Of note, only in schizophrenia a reduced thalamic activation has been reported (Sugranyes et al., 2011).

Collectively, these findings relative to the functioning of social brain network in the two conditions may indicate that ASD and schizophrenia are characterized by shared as well distinctive brain mechanisms underpinning the social dysfunction, even during the similar execution of specific tasks. ASD and schizophrenia show overlapping deficits in theory of mind, eye gaze orienting on faces in social scenes, judgments of trustworthiness from faces, and discrimination of emotion from impoverished “point-light motion displays” (Craig et al., 2004; Sasson et al., 2007; Couture et al., 2010). However, facial affect recognition and social orienting appear more impaired in ASD (Bolte & Poustka, 2003; Sasson et al., 2007).

Computed tomography studies performed on individuals affected by chronic psychoses revealed, as previously mentioned, enlarged ventricular spaces, probably underlying negative symptoms, and hypofrontality. Considering the distinction between deficit and non-deficit schizophrenia, a disruption of white matter tracts has been found only in the deficit subtype of schizophrenia in the right inferior longitudinal fasciculus, the right arcuate fasciculus, and the left uncinate fasciculus, and not in patients with non-deficit schizophrenia and healthy controls. Except this difference, patients with schizophrenia of either subtype were characterized by cortical thickness reductions in similar neuroanatomic patterns in comparison with healthy controls, whereas all three groups did not differ relatively to surface areas and subcortical volumes. Taken together, these findings suggest that white matter tract disruption is a neurobiological feature of the deficit syndrome and reductions in cortical

thickness represent the distinctive feature of patients diagnosed as having schizophrenia (Iritani, 2013; Voineskos et al., 2013).

1.7.4 NEUROPSYCHOLOGICAL FEATURES

From a neuropsychological perspective, several theories aimed to explain ASD focusing on what they considered the underlying core deficit in brain functioning. Therefore, each theory emphasizes one aspect rather than another: central coherence deficit, extreme male brain functioning, theory of mind deficit, executive functions deficit and hypoactivity of the mirror system. The latter emphasizes the role of the mirror neurons, which are considered of fundamental importance for social interaction (Lombardo et al., 2012; Keller et al., 2011b).

In regard to schizophrenia, theories on the extreme male brain functioning and central coherence deficit have not been described; in contrast, they focused on the presence of deficits in sustained attention and working memory as a trait marker of the disorder, and of deficits related to other neuropsychological aspects, such as verbal memory and learning, theory of mind, processing speed, visuospatial processing, motor speed, and language, especially related to negative symptoms (Meltzer, 2004; Kurtz, 2011; Carriòn et al., 2011).

Recently, an altered mirror system has been implicated also in schizophrenia (Enticott et al., 2008; Bertrand et al., 2008; Park et al., 2009; Varcin et al., 2010). Using transcranial magnetic stimulation, Enticott et al. (2008) identified alterations in the mirror neuron system in many individuals with schizophrenia, and this supports the hypothesis of an underlying connectivity deficit at the basis of the disorder, even though that impairment is not as substantial as in autism.

In conclusion, collected findings suggested that autism is underpinned by abnormalities in brain circuitry related to social cognition and communication; instead, in ID cognitive impairments are related to logical-deductive skills. Differences in level and extend of disruption of neural circuits may account the type and the severity of the syndrome (Owen et al., 2011; Owen, 2012).

Table 1. Differences between ID, ASD and SSD (Bertelli et al., 2015)

CLINICAL DATUM	ID	ASD	SSD
ONSET AND AGE OF RECOGNITION	• Before 18 yrs [most severe ID identified in early years while mild ID may not identified until later (e.g., school entry)]	• Any time post natal but key defining features can be traced back to first three years	• First episode of illness in adolescence or early adult life • "at risk" and prodromal mental states. 25-40% convert • Childhood-onset schizophrenia – rare before 7-8 yrs of age

CLINICAL FEATURES AND IQ	• IQ <70 • Often physical stigmata • Clinical features associated with functioning level – mild, moderate, severe, profound	• Triad of impairments: social, communication, repeat. behaviours (sensory abnormalities) • Across all functioning levels • Up to 70% have ID	• Positive symptoms • Negative symptoms • Across all levels of IQ but may be premorbid decline in function
INTEREST TOWARDS OTHERS	variable from case to case	unusually disinterested in shared sense and others' thought	try to guess other's attribution of sense
DELUSIONS	not present	not present (but fantastic thought)	present
HALLUCINATIONS	not present	not present (but sensory abnormalities)	present
ANATOMICAL ANOMALIES OF THE CNS	variable from case to case	diffused gray matter increase and anomalies in the neuroanatomical networks	enlarged ventricular spaces and hypofrontality
PSYCHIATRIC COMORBIDITY	Psychopathology frequent: estimated to be X4 that of the general population	Asperger: mood and anxiety disorders common Autism with ID compared to ID only: • Greater frequency of new onset (episodic) disorders e.g., mood, anxiety, adjustment disorders • Greater frequency of background (non episodic) disorders e.g., ADHD, tics, phobias • Episodic and non episodic disorders co-exist	More recently the focus of research attention (e.g., depression, anxiety)

1.8 AIM

Differential diagnosis between ASD, ID, and SSD IN ID is often challenging especially for the psychiatrist without specific training.

The aim of the research project is to identify some clinical characteristics that relate most with each of the three specific conditions and their combination, which might contribute in turn to the development of better criteria of differential diagnosis and psychiatric comorbidity.

CHAPTER 2

MATERIALS AND METHODS

2.1 Study design

This was a transversal observational descriptive study.

2.2 Participants, procedure and setting

We assessed a sample of 61 adults - 23 women and 38 men – Demographic characteristics of the sample are shown in Table 2 and 3.

The criteria for inclusion in the study were that the participants were age 18 or older at the beginning of the study. Study participants have been randomly or consecutively recruited among those attending the psychiatric services of CREA, the Department of Neurological and Psychiatric Sciences of the University of Florence (DNPS-UF), and two institutes of care attending psychiatric outpatient clinics which are located in Tuscany, with a diagnosis or pervasive features of ASD, ID or SSD according to the Diagnostic Statistical Manual of Mental Disorders 4th edition, Text Revision (DSM-IV-TR; APA, 2000).

The entire sample underwent to a complex psychopathological and anamnestic evaluation, through the administration of the instruments listed below by the candidate and in some case by other collaborators (psychiatrist and psychologist), to the probands themselves or to proxy informants (i.e. family members, educators, social workers, psychologists, or general practitioner), particularly for those with more severe impairment. The candidate attended all sessions of evaluation.

Each patient had to sign an informed consent that allowed the use of their personal data, according to the current legislation on Personal Data Protection. Such consent included a detailed explanation of the study characteristics and purpose.

The assessments were conducted in a quiet, private room for the interview and testing, which lasted approximately one hour for each participant. The interview and assessment consisted of two or three sections, especially in case of participants with ID with more severe impairment accompanied by a caregiver. The assessment scheme was the following: (a) general interview for collecting demographic data; (b) administration of five psychopathology assessment tools; (c) neurocognitive assessment; (d) clinical assessment.

2.3 Assessment tools

- AQ - Autism Spectrum Quotient (Baron-Cohen, 2001)
- EQ - Empathy Quotient (Baron-Cohen & Wheelwright, 2004)

- SPAID-G (Psychiatric Instrument for the Intellectually Disabled Adult-General version; Bertelli, 2012)
- SPAID-DPS (Psychiatric Instrument for the Intellectually Disabled Adult-Pervasive Developmental Disorders; Bertelli, 2012)
- SPAID-P (Psychiatric Instrument for the Intellectually Disabled Adult-Psychotic disorders; Bertelli, 2012)
- WAIS (Wechsler Adult Intelligence Scale; Wechsler, 1955)
- DSM-IV-TR (APA, 2000)
- DC-LD (Diagnostic Criteria for Learning Disabilities; Royal College of Psychiatrists, 2001)
- DM-ID (Diagnostic Manual for Intellectual Disabilities; National Association for Dual Diagnosis, 2007)

1. Psychopathological assessment

Autism Spectrum Quotient (AQ)

The Autism-spectrum Quotient (AQ) is a 50-item questionnaire published in 2001 by Simon Baron-Cohen and his colleagues at the Autism Research Centre at the University of Cambridge, UK. It aims to investigate whether adults of average intelligence have symptoms of autism. Its predominate clinical use is as a screening tool for high-functioning Autism Spectrum Disorders/Asperger Syndrome in adults. The AQ was designed as a self-administered, forced-choice questionnaire for quantifying the number of autistic traits. Reponses are given on a 4-point Likert scale (strongly agree slightly agree, slightly disagree, strongly disagree). Each item scored 1 point for responses suggesting autistic traits either mildly or strongly, and zero otherwise. Basically the range for possible answers is 0 to 50. Scores of 32 or above are one of strong indicators of having as ASD. The questions cover five domains associated with the autism spectrum: social skills, communication skills, imagination, attention to detail, and attention switching/tolerance of change.

Empathy Quotient (EQ)

The Empathy Quotient (EQ) is a 60-item questionnaire (there is also a shorter, 40-item version) of which 40 are clinically relevant and 20 are for distraction only designed to measure empathy in adults. The test was developed by Simon Baron-Cohen and Sally Wheelwright at the Autism Research Centre, University of Cambridge (Baron-Cohen and Wheelwright, 2004). Clinically, the empathy measurements provided by the EQ are used in assessing the level of social impairment. Its predominate clinical use is as a screening tool for high-functioning Autism Spectrum Disorders in adults. The AQ was designed as a self-administered, forced-choice questionnaire. Reponses are given on a 4-point Likert scale (strongly agree slightly agree, slightly disagree, strongly disagree). Score can range from 0 to 80. A cut-off score fewer than 30 was the most useful to differentiate adult with from controls.

In this study we used the Italian version of AQ (Ruta et al., 2011) and EQ questionnaires (Preti et al., 2011).

SPAID project (Psychiatric Instrument for the Intellectually Disabled Adult)

The SPAID project was developed by Marco O. Bertelli in 2007 to screen for psychopathology in adults with intellectual disabilities in response to the scientific need of acquiring a deeper knowledge of the issues related to psychiatric comorbidity in ID, especially in terms of clinical and epidemiological features, and to provide the various professionals working in this field with a tool for psychopathological evaluation able to elaborate a more refined assessment method.

To overcome the limits of other tools in distinguishing single psychiatric disorders, SPAID was designed not as a single instrument but a package of tools, which includes a general version (SPAID-G) used for the preliminary identification of the most important psychopathologic diagnostic areas and area-specific modules helping to carry out a differential diagnosis between disorders belonging to the same group, thus obtaining a defined diagnostic categorization. While the G form does not provide any chronological limits in surveying of symptoms, a large number of items related to the area-specific modules precisely refer to the chronological criteria of DSM syndromes.

All the tools included in the SPAID system – to date SPAID-G, SPAID-DPS for pervasive developmental disorders, SPAID-P for psychotic disorders, SPAID-A for anxiety disorders, and SPAID-U for mood disorders - were constructed considering the possibility of identifying psychiatric symptoms starting from the observation of behaviours, which is the only survey method applicable to all ID cases. The existence of a language disorder must not preclude the patient from expressing his state of suffering on a non-verbal level nor preclude the clinician from making inferences on the basis of the patient's attitudes and behaviours.

SPAID-G

The 52 items that compose the SPAID-G evaluation define behavioural indicators of all the appearing symptoms with different aggregations into the various DSM-IV-TR diagnostic categories. For example, 'to glance at areas where no object is to be perceived and/or to gaze constantly' defines the observational/behavioural indicators of the visual hallucination symptom.

In the calculation process of the current behavioural indicators, the SPAID-G refers to the following meta-syndromic groups of DSM-IV-TR: eating disorders, psychotic disorders, depressive disorder, manic disorder, anxiety disorders, medication side effects, delirium, dementia, substance-related disorders, cluster A (strange) personality disorders, cluster B (dramatic) personality disorders, cluster C (anxious) personality disorders, impulse control disorders, identity disorders, simulation and sexual disorders.

The score for each item is dichotomous (zero or one) according to the presence or absence of the stated behaviour. The score for a symptom may contribute to the scores of different groupings in the same way in which some of the symptoms are transversely present in more than one psychiatric

condition. The score of a grouping becomes relevant and indicates the use of area-specific SPAID, if more than the half of its items are rated as 1. The mean time for administration was 30 minutes.

SPAID-P

The 19 items that compose the SPAID-P evaluation define behavioural indicators of all the appearing symptoms with different aggregations into the DSM-IV-TR diagnostic categories of psychotic disorders. In the calculation process of the behavioural indicators, the SPAID-P refers to the following diagnostic groups of DSM-IV-TR: schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder, and cluster A personality disorder.

The score for each item is dichotomous (zero or one) according to the presence or absence of the stated behaviour. The mean time for administration was 15 minute.

SPAID-DPS

The 12 items that compose the SPAID-DPS evaluation define behavioural indicators of all the appearing symptoms with different aggregations into the DSM-IV-TR diagnostic categories of pervasive developmental disorders. In the calculation process of the behavioural indicators, the SPAID-DPS refers to the following diagnostic groups of DSM-IV-TR: Autism, Rett syndrome, Childhood disintegrative disorder, Asperger syndrome, and PDD-NOS,

The score for each item is dichotomous (zero or one) according to the presence or absence of the stated behaviour. The mean time for administration was 15 minute.

The SPAID-G tool is validated in Italian language (Bertelli et al., 2010; Bertelli et al., 2012).

For a quick calculation of the SPAID scoring, an original software was used in the two available versions for DOS and Windows operating systems.

2. Cognitive assessment

Wechsler Adult Intelligence Scale (WAIS)

The assessment battery is composed of tests relevant to cover intellectual abilities, memory and executive functions.

The Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) is the most commonly administered general intelligence test for adults and is also viewed as a broad assessment of intellectual abilities. It is an individually administered measure of intelligence, intended for adults aged 16–89. It is the best standard and most widely used intelligence test in clinical practice and is intended to measure human intelligence reflected in both verbal and performance abilities. The original WAIS was published in 1955 by David Wechsler, as a revision of the Wechsler-Bellevue Intelligence Scale that had been released in 1939. The last edition of the test (WAIS-IV) was released in 2008 from Pearson. We used in this study the Italian version of the WAIS-R (1981, it. tr. 1997). It consisted of six verbal and five performance subtests. The verbal tests were: information, comprehension, arithmetic, digit span,

similarities, and vocabulary. The Performance subtests were: picture arrangement, picture completion, block design, object assembly, and digit symbol. It provided scores for Verbal IQ, Performance IQ, and Full Scale-Total IQ. The mean time of administration was 60-90 minutes.

The entire sample was subjected to psychopathological assessment through the use of a rating scale for psychodiagnostic orientation, SPAID-G. The entire sample was also evaluated with the SPAID-P and SPAID-DPS. Part of the sample was screened for ASD through the assessment of the Italian adaptations of Baron-Cohen's AQ and EQ (30 participants). The tests were hetero-administered in the case of people with intellectual disabilities.

The entire sample was evaluated for neurocognitive functions through the WAIS-R administration. Sub-areas scores of WAIS-R were available for part of the sample (33 participants). Total IQ score was estimate for the entire sample.

For the entire 61 participants clinical diagnoses were carried out by clinical psychiatrists according to the DSM-IV-TR, DC-LD and DM-ID criteria. Diagnostic Criteria for Learning Disability (DC-LD) (Royal College of Psychiatrists, 2001) and Diagnostic Manual - Intellectual Disability (DM-ID) (Fletcher et al., 2007) are the adaptation of the ICD-10 and DSM-IV-TR tailored for people with produced by The Royal College of Psychiatrists (UK) and the National Association for Dual Diagnosis (USA), respectively.

2.4 Statistical analyses

The statistical analyses were carried out according to the following methods.

The background characteristics were evaluated by the calculation of averages and standard deviations.

For AQ and EQ, the analysis of variance (ANOVA) was used to assess a mean scores comparison between presence and absence of diagnosis at T1.

The SPAID tools score differences were analysed through many different statistical methods. The SPAID-G area mean scores comparison between presence and absence of ID, ASD and SSD diagnoses at T0 and T1 were evaluated by Student's t-test. The ANOVA statistical analysis was used to evaluate the mean scores comparison between presence and absence of diagnosis at T1 for SPAID-G and SPAID-P delusion and hallucination items.

The correlations between SPAID areas in ID, ASD, and SSD groups at Time 1 was estimated through Spearman's R. The calculation of averages and standard deviations was used to evaluate the frequency of SPAID-G items in ID, ASD and SSD groups at Time 1.

The multiple regression block-wise and stepwise were performed to evaluate the relationship between SPAID-G areas and ID, ASD or SSD diagnoses. Hierarchical regression analysis was applied to study the association between SPAID-G areas and both the three diagnoses and age and gender.

The WAIS score differences were analysed using different types of statistical analysis.

The ANOVA was used to assess the comparison between WAIS test mean scores and the presence and absence of diagnosis at T1. The WAIS test mean scores in the total sample were calculated by the average, and standard deviation. The Kruskal-Wallis H test was employed to analyse the differences in WAIS test scores between ID, ASD and SSD at Time 1.

Statistic pack SPSS 16.0 for Windows has been utilized to create and the update database and for further statistical processing of data.

CHAPTER 3

RESULTS

3.1 ID, ASD, and SSD diagnoses at T0 and T1

Comparing the diagnoses at T0 and T1 we found considerable differences. The diagnoses of ID were 37 at T0 and 55 at T1, with an increase of around 149%. The diagnoses of ASD were 27 at T0 and 40 at T1, with a percentage increase of around 148. The diagnoses of SSD were almost the same at T0 and T1, 24 and 28 respectively.

The diagnoses of co-occurrence of ASD in ID passed from 9 at T0 to 36 at T1, with an increase of 400%. The diagnoses of co-occurrence of SSD in ID passed from 7 at T0 to 25 at T1, with an increase of around 357%.

The co-occurrence of ASD and SSD was 1 at T0 and 8 at T1, referred for 7 cases to persons with ID.

3.2 Background characteristics of the sample

A total of 61 participants took part in the study. These comprised 38 males and 23 females with a mean age of 30.82 years. At T0 they included 37 persons with ID, 27 with ASD, and 24 with SSD. In most cases information on the ID degree was unavailable, for lack of inappropriate assessment. Comorbidity between ID, ASD, and/or SSD was found in a few cases, 9 ID + ASD, 7 ID + SSD, and 1 ASD+SSD. Any participant presented co-occurrence of all the three diagnoses.

At T0 background characteristics were not available for most participants, with the exception of gender, age, and, to a lesser extent, education. These have been summarised in Table 2.

At T1 participants with ID were 55. The ID degree was distributed as follows: Borderline Intellectual Functioning (BIF) in 16 participants, mild in 11, moderate in 17, and severe in 4. Only 6 out of the 61 study participants weren't diagnosed with ID. The education level ranged from 5 (Primary school) to 17 years (University) with a mean of 11.13 years. Participants with ASD were 40, with a gender ratio higher than in the other groups: 28 male and 12 female. The ID degree was moderate in the majority of cases. Participants with SSD were 28, with a very high prevalence of borderline ID.

The number of cases presenting ID in comorbidity with ASD or SSD was 36 and 25, respectively.

Participants with ID and co-occurring ASD and SSD were 7, 5 male and 2 female. Their average age was 33.71 years, with a preponderance of borderline intellectual functioning.

Details on background characteristics and co-occurrence of ASD and/or SSD at T1 are shown in Table 3 and 4.

Table 2. Background characteristics in the total sample at T0

	N tot= 61	**ID level** n (%)					**Age** range (mean±s.d.)	**Gender** n (%)		**Educational stage (yrs)** 5=Primary school 17=University range (mean±s.d.)
		Absent	BIF^	Mild	Moderate	Severe		Males	Females	
ID	37	12 (32,4%)	3 (8,1%)	7 (18,9%)	8 (21,6%)	7 (18,9%)	19-58 (31,46±2,12)	19 (70,3%)	6 (29,7%)	5-17 (10,67±0,58)
ASD	27	3 (25%)	0	3 (25%)	3 (25%)	3 (25%)	18-46 (25,19±1,44)	18 (66,7%)	9 (33,3%)	5-17 (11,96±0,43)
SSD	24	9 (56,2%)	1 (6,25%)	1 (6,25%)	3 (18,8%)	2 (12,5%)	19-58 (36,5±2,44)	12 (50%)	12 (50%)	8-17 (11,36±0,60)
ID+ASD	9		0	3 (33.3%)	3 (33.3%)	3 (33.3%)	19-46 (28.33±10.14)	7 (77.8%)	2 (22.2%)	8-13 (11.22±2.43)
ID+SSD	7		1 (14.3%)	1 (14.3%)	3 (42.9%)	2 (28.6%)	22-58 (43.43±12.56)	4 (57.1%)	3 (42.9%)	5-17 (10.33±3.98)
ASD+SSD	1		1 (100%)				19	1 (100%)	-	13
ID+ASD+SSD	0	-	-	-	-	-	-	-	-	-

^ BIF: Borderline Intellectual Functioning

Table 3. Background characteristics in the total sample at T1

	N tot= 61	**ID level** n (%)					**Age** range (mean±s.d.)	**Gender** n (%)		**Educational stage (yrs)** 5=Primary school 17=University range (mean±s.d.)
		Absent	BIF^	Mild	Moderate	Severe		Males	Females	
ID	55		16 (29.1%)	11 (20%)	17 (30.9%)	4 (20%)	18-58 (31.00±10.86)	35 (63.6%)	20 (36.4%)	5-17 (11.13±2.48)
ASD	40	4 (10%)	9 (22.5%)	7 (17.5%)	12 (30%)	8 (20%)	18-58 (28.30±10.38)	28 (70%)	12 (30%)	5-17 (11.44±2.57)
SSD	28	3 (10.7%)	11 (39.3%)	5 (17.9%)	6 (21.4%)	3 (10.7%)	18-58 (34.96±10.65)	15 (53.6%)	13 (46.4%)	8-17 (11.26±2.52)
ID+ASD	36		9 (25%)	7 (19.4%)	12 (33.3%)	8 (22.2%)	18-58 (28.83±10.67)	25 (69.4%)	11 (30.6%)	5-14 (11.26±2.47)
ID+SSD	25		11 (44%)	5 (20%)	6 (24%)	3 (12%)	21-58 (35.16±10.17)	15 (60.%)	10 (40.%)	8-17 (10.92±2.41)
ASD+SSD	8	1 (12.5%)	4 (50%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	19-46 (31.88±11.25)	5 (62.5%)	3 (37.5%)	8-13 (11.50±2.00)
ID+ASD+SSD	7		4 (57.1%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	22-46 (33.71±10.78)	5 (71.4%)	2 (28.6%)	8-13 (11.29±2.05)

Table 4. Total sample background characteristics stratified by intellectual disability degree

		ID level n (%)		**Age** range (mean±s.d.)	**Gender** n (%)		**Educational stage (yrs)** 5=Primary school 17=University range (mean±s.d.)
					Males	Females	
ID	55	BIF	16 (29.1%)	20-58 (35.75±10.72)	12 (75%)	4 (25%)	8-17 (12.56±1.96)
		Mild	11 (20%)	19-46 (30.90±10.40)	6 (54.5%)	5 (45.5%)	8-14 (11.00±2.32)
		Moderate	17 (30.9%)	18-56 (27.65±10.35)	9 (52.9%)	8 (47.1%)	5-13 (10.31±2.62)
		Severe	4 (20%)	19-58 (29.36±11.26)	8 (72.7%)	3 (27.3%)	8-13 (10.30±2.49)
ASD	40	Absent	4 (10%)	19-32 (23.50±6.13)	3 (75%)	1 (25%)	9-17 (13±3.26)
		BIF	9 (22.5%)	20-45 (30.56±9.00)	7 (77.8%)	2 (22.2%)	9-13 (12.56±1.30)
		Mild	7 (17.5%)	19-46 (25.86±9.29)	4 (57.1%)	3 (42.9%)	8-14 (12.14±2.00)
		Moderate	12 (30%)	18-56 (27.33±11.81)	8 (66.7%)	4 (33.3%)	5-13 (10.58±2.93)
		Severe	8 (20%)	19-58 (31.75±12.53)	6 (75%)	2 (25%)	8-13 (9.86±2.41)
SSD	28	Absent	3 (10.7%)	19-52 (33.33±16.92)	0	3 (100%)	13-16 (14.00±1.73)
		BIF	11 (39.3%)	22-58 (39.18±10.64)	8 (72.7%)	3 (27.3%)	8-17 (12.36±2.37)
		Mild	5 (17.9%)	35-46 (41.00±5.09)	2 (40%)	3 (60%)	8-10 (8.80±1.09)
		Moderate	6 (21.4%)	21-36 (27.33±6.43)	2 (33.3%)	4 (66.7%)	8-12 (10.00±1.58)
		Severe	3 (10.7%)	22-34 (26.33±6.65)	3 (100%)	0	8-13 (10.67±2.51)
ID+ASD	36	BIF	9 (25%)	20-45 (30.56±9.00)	7 (77.8%)	2 (22.2%)	9-13 (12.56±1.33)
		Mild	7 (19.4%)	19-46 (25.86±9.29)	4 (57.1%)	3 (42.9%)	8-14 (12.14±2.03)
		Moderate	12 (33.3%)	18-56 (27.33±11.81)	8 (66.7%)	4 (33.3%)	5-13 (10.58±2.93)
		Severe	8 (22.2%)	19-58 (31.75±12.53)	6 (75%)	2 (25%)	8-13 (9.86±2.41)
ID+SSD	25	BIF	11 (44%)	22-58 (39.18±10.64)	8 (72.7%)	3 (27.3%)	8-17 (12.36±2.37)
		Mild	5 (20%)	35-46 (41.00±5.09)	2 (40%)	3 (60%)	8-10 (8.80±1.09)
		Moderate	6 (24%)	21-36 (27.33±6.43)	2 (33.3%)	4 (66.7%)	8-12 (10.00±1.58)
		Severe	3 (12%)	22-34 (26.33±6.65)	3 (100%)	0	8-13 (10.67±2.51)
ASD+SSD	8	Absent	1 (12.5%)	19	0	1 (100%)	13
		BIF	4 (50%)	22-45 (33.50±11.67)	3 (75%)	1 (25%)	9-13 (12.00±2.00)
		Mild	1 (12.5%)	46	0	1 (100%)	8
		Moderate	1 (12.5%)	22	1 (100%)	0	12
		Severe	1 (12.5%)	34	1 (100%)	0	11
ID+ASD+ SSD	7	BIF	4 (57.1%)	22-45 (33.50±11.67)	3 (75%)	1 (25%)	9-13 (12.00±2.00)
		Mild	1 (14.3%)	46	0	1 (100%)	8
		Moderate	1 (14.3%)	22	1 (100%)	0	12
		Severe	1 (14.3%)	34	1 (100%)	0	11

3.3 AQ and EQ

For AQ and EQ only a mean scores comparison between presence and absence of diagnosis at T1 was performed.

For ID, no statistically significant differences were observed between those who received a diagnosis at T1 and those who did not.

Within the ASD group a statistically significant difference was found only for EQ mean scores, while those with SSD presented statistically significant differences for both measures, although to a lesser extent for AQ (see Table 5).

Table 5. AQ and EQ mean scores comparison between presence and absence of diagnosis at T1

	ID		ASD		SSD	
	F	Sig.	F	Sig.	F	Sig.
AQ tot	.276	.891	1.912	.178	7.593	.010
EQ tot	.787	.545	11.267	.002	29.739	.000

*Sig. p≤ 0.05

3.4 SPAID

Being the behavioural equivalents of psychopathological symptoms the main focus of our research, the SPAID tools score differences were analysed through many different statistical methods.

3.4.1 SPAID-G area mean scores comparison between presence and absence of diagnosis at T0

Within the ID group, no statistically significant SPAID-G area mean scores differences were observed between those who received a diagnosis at T0 and those who did not.

For ASD, a statistically significant difference was found for Sexual disorders, Simulation, DOC, and especially Medication side effects mean scores. Those with SSD presented statistically significant differences for Sexual disorders, Medication side effects and Anxiety disorders mean scores, although significance for Sexual disorders and Medication side effects was lower than in those with ASD. Furthermore in SSD a statistically significant difference was found especially for Autism and DOC area mean scores (see Table 6).

Table 6. SPAID-G area mean scores comparison between presence and absence of diagnosis at T0

SPAID-G AREA	ID		ASD		SSD	
	F	Sig.	F	Sig.	F	Sig.
Eating disorders	.907	.472	.932	.339	.073	.789
Psychotic disorders	.681	.610	.000	.998	1.281	.262
Depression	.479	.751	1.473	.230	.012	.914
Mania	1.870	.140	2.324	.133	3.443	.069
Anxiety disorders	1.585	.202	5.042	.029	5.776	.020
Medication side effects	.173	.951	9.327	.003	4.231	.044
Delirium	.748	.567	.012	.913	.312	.579
Dementia	.576	.682	.906	.345	.156	.694
Substance-related disorders	.918	.465	.171	.681	1.662	.203
personality disorders Cluster A (strange)	.903	.474	.574	.452	.884	.351
personality disorders Cluster B (dramatic)	1.026	.409	.714	.402	.782	.380
personality disorders Cluster C (anxious)	.098	.982	.033	.857	3.103	.084
Impulse control disorders	1.388	.260	2.642	.110	.831	.366
Autism	.249	.908	1.948	.168	9.301	.003
Identity disorders	.889	.482	3.278	.075	3.419	.070
Simulation	1.287	.296	7.481	.008	2.910	.093
Sexual disorders	.604	.663	4.640	.035	4.250	.044
DOC	1.699	.190	7.669	.008	10.129	.003

*Sig. p≤ 0.05

3.4.2 SPAID-G area mean scores comparison between presence and absence of diagnosis at T1

For ID, statistically significant SPAID-G area mean score differences were found only for Simulation between those who received a diagnosis at T1 and those who did not.

Participants with ASD presented statistically significant differences for DOC, Sexual, and particularly for Autism mean scores. Within the SSD group, a statistically significant difference was observed especially for DOC mean scores. Furthermore in this latter group statistically significant differences were also found for Identity disorders, Simulation, Depression, Sexual disorders, and Medication side effects (see Table 7).

Table 7. SPAID-G area mean scores comparison between presence and absence of diagnosis at T1

SPAID-G AREA	ID		ASD		SSD	
	F	Sig.	F	Sig.	F	Sig.
Eating disorders	2.356	.065	.266	.608	.602	.441
Psychotic disorders	2.073	.097	1.877	.176	3.497	.066
Depression	1.747	.153	2.875	.095	4.915	.030
Mania	1.042	.394	.066	.799	.015	.904
Anxiety disorders	1.200	.321	1.105	.297	.671	.416
Medication side effects	1.405	.244	3.251	.076	6.425	.014
Delirium	1.184	.328	1.881	.184	2.855	.096
Dementia	2.307	.069	1.229	.272	3.325	.073
Substance-related disorders	1.477	.222	.039	.844	.419	.520
personality disorders Cluster A (strange)	1.390	.249	.201	.656	1.588	.213
personality disorders Cluster B (dramatic)	1.109	.361	.077	.782	.261	.611
personality disorders Cluster C (anxious)	1.116	.358	.074	.786	.785	.379
Impulse control disorders	.999	.416	1.435	.236	2.213	.142
Autism	.660	.622	12.660	.001	3.322	.073
Identity disorders	1.445	.231	1.445	.234	4.130	.047
Simulation	3.083	.023	1.615	.209	4.485	.038
Sexual disorders	1.033	.398	6.270	.015	5.086	.028
DOC	1.825	.144	6.011	.018	23.416	.000

*Sig. p≤ 0.05

3.4.3 Significant Correlations between SPAID areas in ID, ASD, and SSD groups at Time 1

For the ID group, the correlations between SPAID areas resulted in the following frequency: Anxiety Disorders (13 correlations), Substance-related disorders (13), Psychotic disorders (12), Depression (11), Delirium (10), Dementia (10), Mania (9), personality disorders Cluster A (strange) (9), personality disorders Cluster B (dramatic) (8), Impulse control disorders (7), Identity disorders (7), personality disorders Cluster C (anxious) (6), Medication side effects (5), Simulation (5), Eating disorders (3), Autism (2), Sexual disorders (1), and DOC (1) (see Table 8).

For the ASD group: Psychotic disorders (13), Substance-related disorders (13), Depression (11), Anxiety disorders (11), Delirium (10), personality disorders Cluster A (strange) (10), Mania (9), Dementia (9), personality disorders Cluster B (dramatic) (9), Identity disorders (8), Medication side effects (7), Impulse control disorders (7), Simulation (7), personality disorders Cluster C (anxious) (5), Eating disorders (4), DOC (3), and Autism (2). For Sexual disorders we did not find any statistically significant correlation (see Table 9).

Finally, for the SSD: Anxiety disorders (9), Depression (8), Mania (8), Dementia (8), Substance-related disorders (8), Psychotic disorders (7), Delirium (7), personality disorders Cluster A (strange) (6), Impulse control disorders (5), personality disorders Cluster B (dramatic) (4), Medication side effects (3), personality disorders Cluster C (anxious) (3), Simulation (2), Eating disorders (1), and Identity disorders (1). Autism, Sexual disorders, and DOC did not show any significant correlation (see Table 10).

Table 8. Significant Correlations between SPAID areas in ID at Time 1

		Eating disorders	Psychotic disorders	Depression	Mania	Anxiety disorders	Medication side effects	Delirium	Dementia	Substance-related disorders	personality disorders Cluster A	personality disorders Cluster B	personality disorders Cluster C	Impulse control disorders	Autism	Identity disorders	Simulation	Sexual disorders	DOC
Eating disorders	Correl R			.554**			.655**			.362**									
	Sig.			.000			.000			.007									
Psychotic disorders	Correl R			.843**	.698**	.680**	.346**	.846**	.800**	.848**	.622**	.452**	.485**	.419**		.458**			
	Sig.			.000	.000	.000	.010	.000	.000	.000	.000	.001	.000	.001		.000			
Depression	Correl R	.554**	.843**		.496**	.555**	.660**	.697**	.764**	.744**	.616**		.475**			.409**			
	Sig	.000	.000		.000	.000	.000	.000	.000	.000	.000		.000			.002			
Mania	Correl R		.698**	.496**		.706**		.774**	.621**	.846**		.675**		.564**			.371**		
	Sig.		.000	.000		.000		.000	.000	.000		.000		.000			.005		
Anxiety disorders	Correl R		.680**	.555**	.706**			.642**	.541**	.749**	.474**	.563**	.445**	.578**			.436**	.345**	.535**
	Sig.		.000	.000	.000			.000	.000	.000	.000	.000	.001	.000			.001	.010	.001
Medication side effects	Correl R	.655**	.346**	.660**					.407**	.346**									
	Sig.	.000	.010	.000					.002	.010									
Delirium	Correl R		.846**	.697**	.774**	.642**			.765**	.820**	.421**	.471**		.389**		.372**			
	Sig.		.000	.000	.000	.000			.000	.000	.001	.000		.003		.005			
Dementia	Correl R		.800**	.764**	.621**	.541**	.407**	.765**		.666**	.544**		.416**			.380**			
	Sig.		.000	.000	.000	.000	.002	.000		.000	.000		.002			.004			
Substance-related disorders	Correl R	.362**	.848**	.744**	.846**	.749**	.346**	.820**	.666**		.407**	.633**		.593**		.407**	.415**		
	Sig.	.007	.000	.000	.000	.000	.010	.000	.000		.002	.000		.000		.002	.002		
personality disorders Cluster A (strange)	Correl R		.622**	.616**		.474**		.421**	.544**	.407**			.779**		.411**	.348**			
	Sig		.000	.000		.000		.001	.000	.002			.000		.002	.009			
personality disorders Cluster B (dramatic)	Correl R		.452**		.675**	.563**		.471**		.633**				.813**		.445**	.686**		
	Sig.		.001		.000	.000		.000		.000				.000		.001	.000		
personality disorders Cluster C (anxious)	Correl R	.485**		.475**		.445**			.416**		.779**				.484**				
	Sig.	.000		.000		.001			.002		.000				.000				
Impulse control disorders	Correl R		.419**		.564**	.578**		.389**		.593**		.813**					.757**		
	Sig.		.001		.000	.000		.003		.000		.000					.000		
Autism	Correl R										.411**		.484**						
	Sig.										.002		.000						
Identity disorders	Correl R		.458**	.409**				.372**	.380**	.407**	.348**	.445**							
	Sig.		.000	.002				.005	.004	.002	.009	.001							
Simulation	Correl R				.371**	.436**				.415**		.686**		.757**					
	Sig.				.005	.001				.002		.000		.000					
Sexual disorders	Correl R					.345**													
	Sig.					.010													
DOC	Correl R					.535**													
	Sig.					.001													

Spearman R; **. Sig. 0.01 (2-way). N=always ranging from 54 to 55 (38 only for DOC)

Table 9. Significant Correlations between SPAID subarea in ASD at Time 1

		Eating disorders	Psychotic disorders	Depression	Mania	Anxiety disorders	Medication side effects	Delirium	Dementia	Substance-related disorders	personality disorders Cluster A	personality disorders Cluster B	personality disorders Cluster C	Impulse control disorders	Autism	Identity disorders	Simulation	Sexual disorders	DOC
Eating disorders	Correl R			.604**			.646**			.416**			.434**						
	Sig.			.000			.000			.008			.006						
Psychotic disorders	Correl R			.853**	.722**	.736**	.427**	.817**	.785**	.890**	.666**	.576**	.482**	.505**		.552**	.424**		
	Sig.			.000	.000	.000	.006	.000	.000	.000	.000	.000	.002	.001		.000	.006		
Depression	Correl R	.604**	.853**		.545**	.626**	.739**	.713**	.787**	.784**	.669**		.460**			.479**			
	Sig.	.000	.000		.000	.000	.000	.000	.000	.000	.000		.003			.002			
Mania	Correl R		.722**	.545**		.756**		.828**	.621**	.859**		.751**		.607**			.496**		
	Sig.		.000	.000		.000		.000	.000	.000		.000		.000			.001		
Anxiety disorders	Correl R		.736**	.626**	.756**			.761**	.637**	.791**	.481**	.623**		.525**			.472**		.537**
	Sig.		.000	.000	.000			.000	.000	.000	.002	.000		.001			.002		.002
Medication side effects	Correl R	.646**	.427**	.739**					.506**	.413**	.426**					.481**			
	Sig.	.000	.006	.000					.001	.008	.006					.002			
Delirium	Correl R		.817**	.713**	.828**	.761**			.705**	.875**	.412**	.686**		.558**		.481**			
	Sig.		.000	.000	.000	.000			.000	.000	.008	.000		.000		.002			
Dementia	Correl R		.785**	.787**	.621**	.637**	.506**	.705**		.691**	.563**					.513**			
	Sig.		.000	.000	.000	.000	.001	.000		.000	.000					.001			
Substance-related disorders	Correl R	.416**	.890**	.784**	.859**	.791**	.413**	.875**	.691**		.483**	.714**		.627**		.496**	.527**		
	Sig.	.008	.000	.000	.000	.000	.008	.000	.000		.002	.000		.000		.001	.000		
personality disorders Cluster A (strange)	Correl R		.666**	.669**		.481**	.426**	.412**	.563**	.483**			.821**		.625**	.468**			
	Sig.		.000	.000		.002	.006	.008	.000	.002			.000		.000	.002			
personality disorders Cluster B (dramatic)	Correl R		.576**		.751**	.623**		.686**		.714**				.833**		.430**	.724**		.614**
	Sig.		.000		.000	.000		.000		.000				.000		.006	.000		.000
personality disorders Cluster C (anxious)	Correl R	.434**	.482**	.460**							.821**				.624**				
	Sig.	.006	.002	.003							.000				.000				
Impulse control disorders	Correl R		.505**		.607**	.525**		.558**		.627**		.833**					.854**		
	Sig.		.001		.000	.001		.000		.000		.000					.000		
Autism	Correl R										.625**		.624**						
	Sig.										.000		.000						
Identity disorders	Correl R		.552**	.479**			.481**	.481**	.513**	.496**	.468**	.430**							
	Sig.		.000	.002			.002	.002	.001	.001	.002	.006							
Simulation	Correl R		.424**		.496**	.472**				.527**		.724**		.854**					.501**
	Sig.		.006		.001	.002				.000		.000		.000					.003
Sexual disorders	Correl R																		
	Sig.																		
DOC	Correl R					.537**						.614**					.501**		
	Sig.					.002						.000					.003		

Spearman R; **. Sig. 0.01 (2-way). N=always is 40 (39 only for DCA and 32 only for DOC)

Table 10. Significant Correlations between SPAID subarea in SSD at Time 1

		Eating disorders	Psychotic disorders	Depression	Mania	Anxiety disorders	Medication side effects	Delirium	Dementia	Substance-related disorders	personality disorders Cluster A (strange)	personality disorders Cluster B (dramatic)	personality disorders Cluster C (anxious)	Impulse control disorders	Autism	Identity disorders	Simulation	Sexual disorders	DOC
Eating disorders	Correl R						.497**												
	Sig.						.007												
Psychotic disorders	Correl R			.833**	.749**	.738**		.867**	.736**	.882**	.608**								
	Sig.			.000	.000	.000		.000	.000	.000	.001								
Depression	Correl R		.833**		.518**	.625**	.675**	.770**	.741**	.743**	.609**								
	Sig.		.000		.005	.000	.000	.000	.000	.000	.001								
Mania	Correl R		.749**	.518**		.566**		.711**	.516**	.839**		.563**		.598**					
	Sig.		.000	.005		.002		.000	.005	.000		.002		.001					
Anxiety disorders	Correl R		.738**	.625**	.566**			.569**	.487**	.688**	.497**		.504**	.492**					
	Sig.		.000	.000	.002			.002	.009	.000	.007		.006	.008					
Medication side effects	Correl R	.497**		.675**					.514**										
	Sig.	.007		.000					.005										
Delirium	Correl R		.867**	.770**	.711**	.569**			.795**	.747**	.550**								
	Sig.		.000	.000	.000	.002			.000	.000	.002								
Dementia	Correl R		.736**	.741**	.516**	.487**	.514**	.795**		.598**	.623**								
	Sig.		.000	.000	.005	.009	.005	.000		.001	.000								
Substance-related disorders	Correl R		.882**	.743**	.839**	.688**		.747**	.598**			.519**		.551**					
	Sig.		.000	.000	.000	.000		.000	.001			.005		.002					
personality disorders Cluster A (strange)	Correl R		.608**	.609**		.497**		.550**	.623**				.748**						
	Sig.		.001	.001		.007		.002	.000				.000						
personality disorders Cluster B (dramatic)	Correl R				.563**					.519**				.795**			.721**		
	Sig.				.002					.005				.000			.000		
personality disorders Cluster C (anxious)	Correl R					.504**					.748**					.513**			
	Sig.					.006					.000					.005			
Impulse control disorders	Correl R				.598**	.492**				.551**		.795**					.705**		
	Sig.				.001	.008				.002		.000					.000		
Autism	Correl R																		
	Sig.																		
Identity disorders	Correl R												.513**						
	Sig.												.005						
Simulation	Correl R											.721**		.705**					
	Sig.											.000		.000					
Sexual disorders	Correl R																		
	Sig.																		
DOC	Correl R																		
	Sig.																		

Spearman R; **. Sig. 0.01 (2-way). N=always 28

3.4.4 Frequency of SPAID-G items in ID, ASD and SSD groups at Time 1

Some SPAID-G items were scored positive much more than others in one, two or all the three diagnostic groups. The item 2 (psychomotor agitation and/or restlessness) and the item 8 (unjustified irritation/opposition) showed the higher scores in all the three diagnostic groups. The items 7 (loss of satisfaction or pleasure for activities or objects) and 16 (avoidance or escape from certain objects, people or situations) were frequent in ID and SSD groups, but not in ASD; while the item 9 (indifference or lack of emotions) was less frequent in SSD.

The item 13 (aggressiveness, both physical and verbal, toward other people or objects) was quite frequent across ID levels, but not in ASD and SSD groups.

For ID, the item 26 (difficulty in making sequences of actions, and disorganized behaviour) and 29 (attitudes of mistrust of others and/or behaviours supported by unjustified hostility) showed the highest scores in Mild ID level, and the item 27 (passing from one action to another without completing any or independently from the environmental context), 32 (indecision between more choices or excessive rigidity towards objects position or the way of doing things) and 33 (inappropriate reactions to the suffering of the people or to the environmental emotional mood) showed the highest scores in Moderate ID degree. An additional interesting finding is that ID, especially the Mild level, was the group with the highest number of positive-scored items. Details are reported in Table 11.

Table 11. Frequency of SPAID-G items in ID, ASD and SSD groups at Time 1

SPAID-G ITEM	ID				ASD	SSD
	Borderline ID	mild ID	moderate ID	severe ID		
item 1	12	4	11	7	21	18
item 2	15	9	15	11	37	25
item 3	9	4	12	5	17	19
item 4	6	4	9	7	18	11
item 5	11	5	8	5	18	17
item 6	4	1	2	1	5	6
item 7	13	5	13	6	23	24
item 8	13	9	14	10	31	23
item 9	12	9	11	8	34	16
item 10	5	5	8	3	18	10
item 11	7	5	7	5	13	13
item 12	3	1	0	1	3	3
item 13	8	8	15	8	27	17
item 14	4	5	7	4	17	9
item 15	10	4	12	8	25	16
item 16	11	7	12	8	29	20
item 17	6	2	4	0	8	11
item 18	5	2	2	0	6	9
item 19	5	2	0	0	6	7
item 20	10	3	5	1	12	13
item 21	5	1	8	2	5	15
item 22	5	1	7	5	14	9
item 23	11	3	11	6	23	15

item 24	5	6	10	4	20	8
item 25	8	5	8	6	25	7
item 26	8	8	12	1	24	15
item 27	6	5	13	3	21	13
item 28	6	5	7	1	12	11
item 29	9	8	6	2	15	15
item 30	6	4	4	6	14	11
item 31	9	6	10	5	19	17
item 32	10	6	14	5	31	13
item 33	8	7	14	8	29	16
item 34	13	7	8	7	27	18
item 35	6	4	8	6	15	16
item 36	10	7	9	8	23	17
item 37	11	6	10	7	24	19
item 38	12	6	12	5	25	18
item 39	4	4	13	4	18	8
item 40	8	5	10	4	17	18
item 41	7	0	4	5	12	5
item 42	7	7	8	4	18	10
item 43	10	5	8	6	18	18
item 44	9	2	10	1	13	15
item 45	4	6	8	3	16	8
item 46	7	2	5	3	13	7
item 47	3	1	5	2	9	7
item 48	2	2	2	1	4	3
item 49	10	8	6	5	23	15
item 50	4	4	10	3	14	11
item 51	0	3	3	1	4	3
item 52	9	6	7	6	25	10
item 53	2	0	1	0	3	1
item 54	2	1	1	0	5	4
item 55	0	0	1	1	2	0

3.4.5 Mean scores comparison between presence and absence of diagnosis at T1 for SPAID-G and SPAID-P delusion and hallucination items

In the ID group, no statistically significant mean score differences were found for SPAID-G and SPAID-P delusion and hallucination items between those who received a diagnosis at T1 and those who did not.

Within both the ASD and SSD groups, a statistically significant difference was found for SPAID-P items 1 (arbitrarily attribution of cause-effect links) and 2 (maintaining a listening position and/or responding to sounds or voices not audible by others) mean scores (see Table 12), with higher scores in those who received a diagnosis at T1 compared with those who did not.

Table 12. SPAID-G and SPAID-P delusion and hallucination items comparison between presence and absence of diagnosis at T1

SPAID-G and SPAID P ITEM°	ID		ASD		SSD	
	F	Sig.	F	Sig.	F	Sig.
SPAID-G item 20	3.139	.021	2.984	.089	1.668	.202
SPAID-G item 29	2.141	.088	3.377	.071	1.210	.276
SPAID-P item 1	.508	.730	21.005	.000	19.968	.000
SPAID-P item 7	2.099	.094	.003	.956	.993	.323
SPAID-G item 3	1.134	.350	4.836	.032	5.177	.027
SPAID-G item 4	1.972	.111	.261	.611	.229	.634
SPAID-P item 2	.485	.747	14.875	.000	12.912	.001
SPAID-P item 3	2.221	.079	.519	.474	1.974	.166
SPAID-P item 4	.348	.844	.280	.599	4.891	.031

*Sig. p≤ 0.005
° G 20 and P 1: arbitrarily attribution of cause-effect links
G 29 and P 7: attitudes of mistrust of others and/or behaviours supported by unjustified hostility
G 3 and P 2: maintaining a listening position and/or responding to sounds or voices not audible by others
G 4 and P 3: to cast the glance towards spaces where there are no objects to see or to gaze
P 4: behaviours attributable to strange tactile or kinesthetic perceptions (such as to look the body with worry, scratching, hitting, or to communicate strange pain

3.4.6 Multiple Regression block-wise

In this statistical elaboration the three groups were treated as Independent Variables (IV) and the SPAID-G area as Dependent Variables (DV). The IV presented a multiple correlation (R) with the DV. The variance is indicated by R-square, while the corrected (for the degrees of freedom) R-square provides an estimate of the efficiency. The presence of autocorrelation between residuals was examined through the Durbin-Watson index, which ranged between 0 and 4, with negative correlations under 2.

The statistical significance (Sig.) for the three groups corresponds to R that allows to see which IV is more important.

The model was found not statistically significant (p >.005) in many cases, but for the relation between DOC subarea and SSD group. For most cases, although the model was not significant, ID was the group with the higher weight.

Table 13. SPAID-G area Multiple Regression block-wise

SPAID-G AREA	R	R square	Sig. F change	Durbin-Watson	Sig.		
					ID_T1	ASD_T1	SSD_T1
Eating disorders	.325	.105	.098	1.881	.017	.869	.524
Psychotic disorders	.265	.070	.242	1.961	.355	.976	.204
Depression	.301	.090	.141	1.864	.370	.878	.157
Mania	.201	.040	.499	1.752	.149	.584	.614
Anxiety disorders	.208	.043	.466	1.735	.229	.483	.968
Medication side effects	.229	.229	.065	2.295	.262	.999	.081
Delirium	.222	.049	.404	2.048	.693	.850	.308
Dementia	.235	.055	.352	1.825	.827	.794	.155
Substance-related disorders	.224	.050	.399	1.933	.124	.659	.427
personality disorders Cluster A (strange)	.183	.034	.581	1.860	.879	.522	.189
personality disorders Cluster B (dramatic)	.244	.059	.317	2.189	.074	.954	.716
personality disorders Cluster C (anxious)	.134	.018	.790	1.910	.875	.607	.330
Impulse control disorders	.250	.063	.293	2.379	.214	.806	.409
Autism	.440	.193	.006	1.875	.508	.003	.381
Identity disorders	.269	.072	.231	2.390	.583	.763	.115
Simulation	393	.155	.022	2.147	.022	.818	.106
Sexual disorders	331	.110	.083	.110	.528	.212	.517
DOC	.599	.359	.000	2.334	.890	.804	.000

*Sig. p≤ 0.005

3.4.7 Multiple Regression stepwise.

In this elaboration the three groups are treated as Independent Variables (IV) and the SPAID-G area as Dependent Variables (DV). The procedure followed for this elaboration is the same used for the regression block-wise, but for the inclusion or removal of one independent variable at each step instead of blocks of variables.

The diagnosis of ID resulted to impact on the score variation of the Eating disorders and Simulation areas, while that of ASD on the score variation of the Autism, and Sexual disorder areas. Furthermore, the diagnosis of SSD was found to influence the score variation of the Depression, Medication side effects, Identity disorders, and DOC areas.

Both ID and SSD groups resulted to impact on the score variation of the Simulation area.

Table 14. SPAID-G area Multiple Regression stepwise

SPAID-G AREA	R	R square	Sig. F change	Durbin-Watson	Sig.		
					ID_T1	ASD_T1	SSD_T1
Eating disorders	.310	.096	.016	1.880	.016		
Psychotic disorders	-	-	-	-	-	-	-
Depression	.277	.077	.030	1.909			.030
Mania	-	-	-	-	-	-	-
Anxiety disorders	-	-	-	-	-	-	-
Medication side effects	.313	.098	.014	2.320			.014
Delirium	-	-	-	-	-	-	-
Dementia	-	-	-	-	-	-	-
Substance-related disorders	-	-	-	-	-	-	-
personality disorders Cluster A (strange)	-	-	-	-	-	-	-
personality disorders Cluster B (dramatic)	-	-	-	-	-	-	-
personality disorders Cluster C (anxious)	-	-	-	-	-	-	-
Impulse control disorders	-	-	-	-	-	-	-
Autism	.420	.177	.001	1.919		.001	
Identity disorders	.256	.065	.047	2.349			. 047
Simulation	.295	.087	.021	2.147	.021		.037
	.392	.154	037				
Sexual disorders	.310	.096	.015	.121		.015	
DOC	.598	.358	.000	2.358			.000

*Sig. p≤ 0.05

3.4.8 Multiple Regression hierarchical

In this elaboration the first step was to input the age and gender variables, and the second step was to input the three groups (IV) one at a time, to see the impact on the SPAID-G areas.

The only area for which a model significance was found is that of DOC, in which the diagnosis of SSD at T1 resulted to significantly impact on the score.

For age and gender we did not find any significant impact, but for the area of Medication side effects, where age has a slight correlation, even if within a non-significant model.

For other areas, although the models were not significant, ID related higher with Eating disorders and Simulation.

Table 15. SPAID-G area Multiple Regression hierarchical

SPAID-G AREA	R	R square	Sig. F change	Durbin-Watson	Sig.				
					ID_T1	ASD_T1	SSD_T1	Age	Gender
Eating disorders	.344	.118	.571	1.892	.023	.953	.571	.765	.383
Psychotic disorders	.281	.079	.178	1.952	.355	.898	.178	.536	.821
Depression	.319	.102	.215	1.831	.428	.884	.215	.458	.629
Mania	.271	.073	.449	1.835	.124	.659	.449	.168	.769
Anxiety disorders	.254	.064	.932	1.757	.248	.615	.932	.540	.427
Medication side effects	.451	.204	.184	2.239	.343	.882	.184	.019	.507
Delirium	.243	.059	.279	2.044	.710	.759	.279	.639	.622
Dementia	.249	.062	.135	1.840	.796	.843	.135	.529	.949
Substance-related disorders	.238	.057	.377	1.965	.124	.715	.377	.545	.989
personality disorders Cluster A (strange)	.267	.072	.222	1.709	.995	.651	.222	.660	.142
personality disorders Cluster B (dramatic)	.281	.079	.782	2.189	.060	.956	.782	.650	.299
personality disorders Cluster C (anxious)	.190	.036	.272	1.847	.873	.728	.272	.436	.624
Impulse control disorders	.253	.064	.411	2.362	.222	.778	.411	.897	.839
Autism	.491	.241	.280	1.834	.540	.007	.280	.296	.190
Identity disorders	.368	.135	.178	2.472	.614	.527	.178	.248	.170
Simulation	.457	.209	.167	2.313	.012	.908	.167	.197	.104
Sexual disorders	.350	.122	.630	.127	.523	.274	.630	.449	.752
DOC	.615	.378	.002	2.420	.923	.679	.002	.578	.414

*Sig. p≤ 0.05

3.5 WAIS-R

Being the difference in cognitive functions between the three groups one of the main focus of our research, the WAIS score differences were analysed using different types of statistical analysis.

3.5.1 WAIS test mean scores comparison between presence and absence of diagnosis at T1

For ID, statistically significant mean scores differences were found for all the WAIS subtests between those who received a diagnosis of ID at T1 and those who did not, but for the subtest of Block design. ASD and SSD groups presented statistically significant differences only for the subtest of Digit symbol (see Table 16).

Table 16. WAIS test mean scores comparison between presence and absence of diagnosis at T1

WAIS TEST	ID		ASD		SSD	
	F	Sig.	F	Sig.	F	Sig.
Information	12.942	.000	.070	.794	.073	.789
Digit span	4.926	.004	.554	.462	.413	.525
Vocabulary	7.643	.022	.882	.095	.247	.623
Arithmetic	23.623	.000	.110	.743	.576	.454
Comprehension	12.505	.001	.564	.459	1.435	.241
Similarities	9.673	.000	.035	.852	.901	.350
Picture completion	6.197	.000	1.303	.262	.763	.389
Picture arrangement	24.544	.000	.536	.470	.015	.904
Block design	19.290	.137	.037	.848	.435	.514
Object assembly	12.552	.000	.995	.326	.074	.788
Digit symbol	1.910	.000	5.424	.027	4.952	.033

*Sig. p≤ 0.05

3.5.2 WAIS test mean scores in the total sample

The ID group scored lower than the other groups in all subtests. A less marked difference was found for the Digit symbol.

Comparing the other two groups, the main score differences were identified in the Digit span, Picture completion, Object assembly, and Digit symbol subtests. For all these, the ASD group scored higher than the SSD, but for the Digit symbol. Details are reported in Table 17.

Table 17. WAIS test mean scores in the total sample

WAIS TEST	ID mild + moderate + severe (mean ± sd)		ASD (mean ± sd)		SSD (mean ± sd)	
	Valid N 13 (33.3%)	Missing N 26 (66.7%)	Valid N 17 (42.5%)	Missing N 23 (57.5%)	Valid N 19 (67.9%)	Missing N 9 (32.1%)
Information	2.46 ± 1.854		6.18 ± 3.610		6.16 ± 4.153	

Digit span	2.92 ± 2.722	7.00 ± 4.569	6.37 ± 3.905
Vocabulary	2.38 ± 1.044	4.76 ± 3.153	5.05 ± 2.877
Arithmetic	1.54 ±.660	4.82 ± 3.358	5.00 ± 3.197
Comprehension	1.77 ± .927	5.41 ± 3.890	5.58 ± 3.990
Similarities	2.69 ± 1.702	6.06 ± 4.451	6.47 ± 3.850
Picture completion	2.77 ± 1.092	6.82 ± 4.419	5.53 ± 3.238
Picture arrangement	1.92 ± 1.320	5.88 ± 4.060	5.47 ± 3.116
Block design	1.62 ± .961	4.94 ± 3.960	4.89 ± 3.710
Object assembly	2.00 ± 1.581	6.06 ± 4.657	5.16 ± 4.018
Digit symbol	2.15 ± 1.519	2.53 ± 1.419	3.68 ± 2.136
Verbal IQ	56.54 ± 5.010	77.41 ± 17.557	75.53 ± 17.855
Performance IQ	55.85 ± 7.116	74.53 ± 16.934	72.16 ± 17.180
Total IQ	52.23 ± 2.46	73.76 ± 17.177	71.74 ± 17.704

3.5.3 Significant Differences in WAIS test scores between ID, ASD and SSD at Time 1

A Kruskal-Wallis H test was run to identify differences in WAIS subtest score between groups. Distributions of Block Design scores were not similar for all groups, as assessed by visual inspection of a boxplot. The distributions of Block design score were statistically different between groups, $\chi2(6) = 13.050$, $p = .042$. Those with ID, alone or in association with ASD or SSD, scored significantly lower than those with ASD or SSD alone. The performance was poorer in ASD than in SSD, both for the conditions themselves and for their association with ID (see Picture 1).

The distributions of Verbal and Performance IQ scores were statistically different between groups, $\chi2(6) = 12.876$, $p = .045$ and $\chi2(6) = 13.760$, $p = .032$ respectively. Again the group with ID, alone or in association with ASD or SSD, scored significantly lower than the other two groups. The score was lower in SSD than in ASD, both for the conditions themselves and for their association with ID (see Picture 2 and 3).

The distributions of Total IQ score were statistically significantly different between groups, $\chi2(6) = 19.044$, $p = .004$. Those with ID, alone or in association with ASD or SSD, scored significantly lower than those with ASD or SSD alone. The score was higher in ASD than in SSD, but the trend reversed when these conditions were associated with ID (see Picture 4).

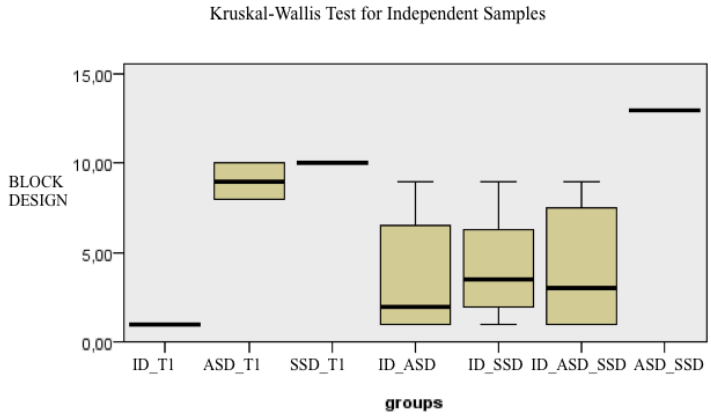
Difference statistical significances are detailed in Table 18.

Table 18. Significant Differences in WAIS test scores between ID, ASD and SSD at Time 1

WAIS TEST	Sig.
Information	.116
Digit span	.291
Vocabulary	.340
Arithmetic	.059
Comprehension	.059
Similarities	.089
Picture completion	.372
Picture arrangement	.071
Block design	.042
Object assembly	.054
Digit symbol	.258
Verbal IQ	.045
Performance IQ	.032
Total IQ	.004

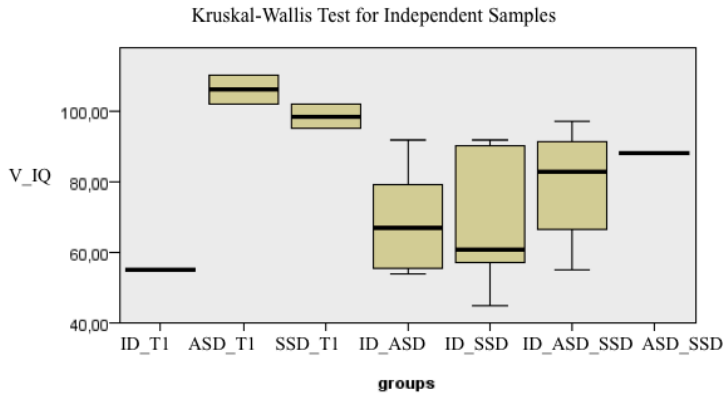
*Sig. $p \leq 0.05$

Picture 1. Distributions of Block design scores by groups



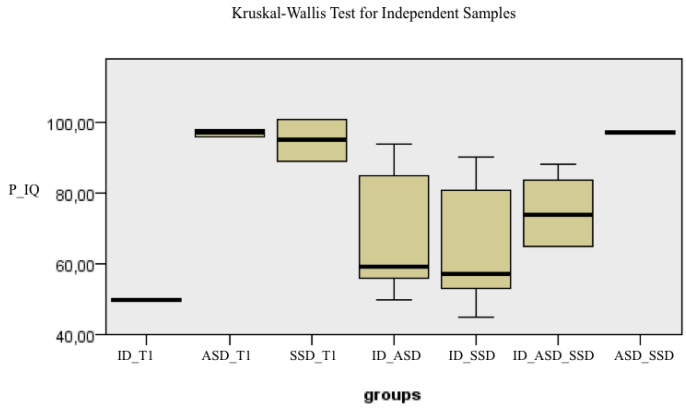
Total number of cases	33
Statistical Test	13,050
Degrees of freedom	6
Asymptotic significance (Sig. 2-way)	,042

Picture 2. Distributions of Verbal IQ scores by groups



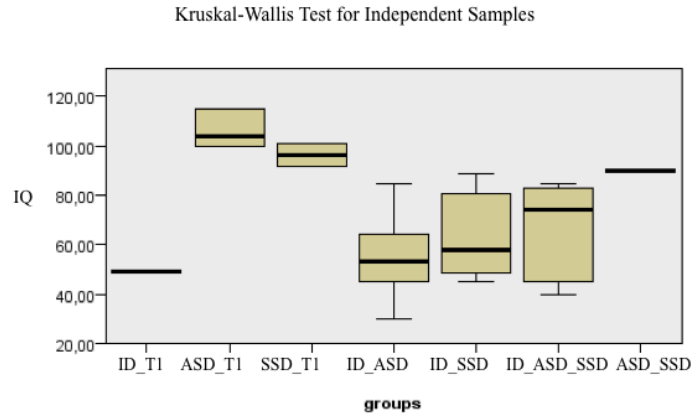
Total number of cases	31
Statistical Test	12,876
Degrees of freedom	6
Asymptotic significance (Sig. 2-way)	,045

Picture 3. Distributions of Performance IQ scores by groups



Total number of cases	31
Statistical Test	13,760
Degrees of freedom	6
Asymptotic significance (Sig. 2-way)	,032

Picture 4. Distributions of Total IQ scores by groups



Total number of cases	60
Statistical Test	19,044
Degrees of freedom	6
Asymptotic significance (Sig. 2-way)	,004

CHAPTER 4

DISCUSSION

As far as our knowledge, which includes the above mentioned literature mapping, this is the first study aimed at identifying the clinical characteristics that relate most with ASD, SSD and their co-occurrence in ID by using a combination of ID-specific neuropsychological and psychopathological assessment tools. Although the small sample size, our study provides new useful indications on how psychiatric specific instrumental assessment can improve the diagnostic sensitivity for the co-occurrence of ASD and/or SSD in ID, but also for BIF, and ID itself. Furthermore it identifies new specific single and clustered behavioural equivalents of psychiatric symptoms, with pathognomonic value.

ID-specific diagnostic process

Previous literature findings already indicated assessment tools and diagnostic approaches tailored for people with ID to be quite useful in differentiating between ASD, ID and SSD (Unenge Hallerbäck et al., 2012), allowing a better understanding of the impact of the ID itself (e.g. cognitive fragmentation associated with stressful life events) on the clinical presentation (Loos & Loss, 2004; Shah & Wing, 2006; Bradley et al., 2011b), as well as an understanding of the context in which the symptoms appear (Hubert & Hollins, 2006).

Autism Quotient and Empathy Quotient

Our results showed that the Autism-spectrum Questionnaire (AQ) and Empathy Questionnaire (EQ), which are screening tools for autism features, were more correlated with SSD than with ASD, with the latter scoring lower than SSD. One possible explanation for this apparently paradoxical result is that these tools, which were created for the high-functioning autism, might not be sensitive enough for the conditions with more severe symptoms, which represented the larger part of our sample. This finding is in line with previous studies illustrating that given the impaired introspective capacities and the different degrees of self-evaluation skills of individuals with ASD, AQ and EQ are not suitable to differentiate between ASD and other diagnoses (Naito et al., 2010; Kästner et al., 2015), particularly within the wide group of relational disorders.

The mismatch between AQ and ASD raises a general issue on how the enlargement of psychiatric features comprised in the autism spectrum for screening purposes may have potential negative impact on research and clinical resources for those autistic syndromes more reliable with Kanner's descriptions or associated with lower personal functioning profiles and different level of ID (Bertelli, 2016).

Co-occurrence of psychiatric disorders (SPAID-G areas)

The screening for psychiatric co-occurrence through the SPAID-G revealed higher scores for Simulation in the presence of diagnosis of ID or SSD, for DOC and Sexual disorders in ASD and SSD, while Identity disorders, Depression, and Medication side effects were specifically higher in SSD. In general, these frequently high scored psychopathological areas can be interpreted as the areas with greater confounding effect on the diagnostic procedure in people with ID. Specific associations may indicate that some behavioural equivalents of psychopathological symptoms are interpreted by the majority of informants or raters as syndromic additional symptoms or alternative expressions of core features. This may happen for symptoms of Simulation, Sexual disorders, DOC and especially Medications side effects in those with ASD, for symptoms of Medications side effects, Sexual disorders, Anxiety disorders and especially Autism and DOC in those with SSD.

ID is the diagnosis with the greatest number of correlations with SPAID-G areas. This might indicate a low specificity of many SPAID-G items for this diagnostic group. Most informants or raters seem to score positive many behavioural equivalents of different psychiatric syndromes every time they think that a psychiatric disorder is co-occurring or has co-occurred with ID. An alternative explanation is that the cognitive impairment (ID dimension) is associated with a broad psychopathological vulnerability more than relational difficulties (ASD and SSD).

The level of specificity for the different psychopathological domains is one major question that arises from the use of all screening tools, even in the general population and in the cases in which tools are aimed at detecting a unique pathological dimension (Cruz et al., 2013). This is particularly evident in the field of ID, since the way people with ID present the specific psychiatric symptoms codified in the general is still far to be defined. All the psychopathological screening tools designed for this population have reported similar problems (Hatton & Taylor, 2008; Myrbakk & von Tetzchner, 2008b).

An attempt to increase the SPAID-G sensitivity is already in progress, by the provision of very detailed descriptions of the item meanings and examples of appropriate informant reports.

The multiple regression block-wise analysis shows a relationship between SSD and DOC symptoms. These results are consistent with the previous researches in the general population, which show that DOC symptoms can occur or more frequently alternate with schizophrenic phases and may have a protective effect against psychotic disintegration (Stengel, 1945; Guillem et al., 2009). Therefore, being the SPAID-G a screening tool referring to the person's life-span, without chronological limits, the association between SSD and DOC found by our statistical elaboration could express this clinical alternation across time.

The multiple regression stepwise points out a strong relation between ID, Eating disorders and Simulation, while the ASD group results more linked to Sexual disorders. For SSD, although the relative high number of correlations, no substantial psychopathological link can be confirmed after the

exclusion of DOC for the above mentioned reasons, and the symptoms clusters which can represent some expressive phases or symptomatologic portions of SSD themselves.

This regression analysis also confirms the finding of previous statistical elaborations on the strong relationship of ID and SSD with the SPAID-G Simulation area score. This could indicate that informants and raters often tend to interpret the behavioural changes they observe in people with ID and ID+SSD as a way to catch someone's attention or to reach other secondary advantages. In the literature feigning and malingering are reported to be often overestimated in patients with schizophrenia or ID, among the latters this misinterpretation is most frequent in case of comorbid psychiatric diagnoses (Weiss et al., 2011; van Impelen et al., 2014).

The multiple regression hierarchical reiterates the already discussed relationships with Eating disorders and Simulation for ID, and with DOC for SSD. This analysis also points out an interesting link between Medications side effects and Age, which means that for people with ID, with or without co-occurrence of ASD or SSD, the possibility to present side effects for any kind of pharmacological treatment increases as long as they grow older. One possible explanation for this relation is that in people with ID the getting older is associated in turn to an increase of the number of pharmacotherapies.

Specific symptoms (SPAID items)

For the identification of specific behaviour equivalents of symptoms to support the clinical differentiation between autism and schizophrenia in ID, any relevant result was reached. 'Irritability', 'agitation', and 'switching from one action to another' resulted to be very unspecific epiphenomena. In SSD and ID, 'indifference or lack of emotions' (SPAID-G item n. 9) was rated as present much less frequently than in ASD, so in case of diagnostic doubt whether it is ASD or SSD, the score 1 in this item should orientate towards the former. On the contrary, 'avoidance' or 'escape' (item n. 16) resulted much more frequent in SSD than in ASD, the same for 'loss of satisfaction or pleasure' (item n. 7), even if to a lesser extent.

Irritability, agitation, aggressiveness, hyperactivity, impulsivity, and other behaviours that are quite common in ID have been repeatedly reported to be associated with different psychiatric disorders (Hurley, 2008; Bertelli et al., 2012; King et al., 2014; Matson & Williams, 2014). Moreover, there are few standardized norms or guidelines in the classification systems for identifying "normal" or "usual" amounts of irritability, hyperactivity and impulsivity in persons with ID.

The SPAID-G and SPAID-P delusion and hallucination items mean score comparison between presence and absence of a specific diagnosis at T1 revealed a statistically significant difference only for SPAID-P items 1 (arbitrarily attribution of cause-effect links) and 2 (maintaining a listening position and/or responding to sounds or voices not audible by others) in the ASD and SSD groups. Surprisingly other items related to visual and tactile/kinesthetic hallucinations, like 'casting the glance to areas where there are no objects to see and/or repeatedly gazing', and 'positions or behaviours

attributable to strange tactile or kinesthetic perceptions' (item n. 3 and 4) were not associated with SSD. This might be due to the informants' higher difficulty of recognising these kinds of hallucination and to the scarce information on prevalence and presentation of this symptoms. Even for the general population, literature on disperceptive phenomena in psychotic disorders mostly refers to auditory hallucinations, which are also reported as the most frequent hallucinations (Chaudhury, 2010). Basing on these results, the SPAID-P is undergoing a process of implementation to increase its sensitivity to the behavioural equivalents of non-auditory hallucinations.

Also 'suspiciousness' and 'hostility', (SPAID-G item n. 29 and SPAID–P item n. 7) did not result to be associated with the diagnosis of SSD, but this is in line with findings in the general population. They are considered rare symptoms and their presence is not necessary to make a diagnosis of psychotic disorder. Furthermore, in both SPAID-G and SPAID-P these two symptoms are included in the same item, which might induce informants and raters to score 1 only in the case in which they are both presents. Also this limit is being addressed in the implementation of the SPAID-P.

Wechsler Adult Intelligence Scale

The comparison of WAIS general, verbal, performance, and subtest scores between the study groups provided very interesting indications. The first refers to the Digit symbol subtest, which was found to be strongly related to the diagnosis of ASD and SSD at T1.

This task, which has not changed since its introduction a century ago, expresses the coordination and speeded performance of a number of scanning, matching and motor operations. Our finding is consistent with the literature, which reports poor digit symbol performances in schizophrenia (Dickinson, 2008; Meier et al., 2014) and ASD (Lincoln et al., 1995; Spek et al., 2007; Goldstein et al., 2008), hypothesising a superficial working memory dysfunction in number-symbol association as the main cause (Nakahachi et al., 2006). The literature also concludes that simple measures of this kind may discriminate people with schizophrenia and autism from control samples better than more widely studied neuropsychological instruments (Lincoln et al., 1995; Spek et al., 2007; Goldstein et al., 2008).

Our finding suggests the Digit symbol test score to be a useful indicator of the co-occurrence of ASD or, to a lesser extent, SSD with ID. It might also orientate for a broad neurodevelopmental disorders, for which a unique major diagnosis is hardly definable.

Through the Kruskal-Wallis statistical analysis we found that the WAIS subtest that appears to discriminate more for the presence of ID is the Block design. This was also the subtest to have statistically significant differences between groups. Those with ID, alone or in association with ASD or SSD, scored significantly lower than those with ASD or SSD alone. ASD had a slightly worse performance than SSD, both for the conditions themselves and for their association with ID.

The performance on this test is indicative of the functioning of the cerebral parietal and frontal lobes. It is considered one of the best measures of spatial ability and spatial visualization, although it is

subject to certain problems of administration, such as anxiety or over-cautious responding. The literature displays impairment in block design performance among schizophrenic populations, while superior performance of autistic individuals are reported (Shah & Frith, 1993; Frith, 2003; De Boer et al., 2014). Some authors indicated better performance in construction time for unsegmented version of the task and persons with higher general functioning (Goldstein et al., 2002; Caron et al., 2006; Stewart et al., 2009).

According to our results, relatively lower scores on Block design supports the exclusion of co-occurrence of ASD and particularly SSD with ID.

The distributions of Verbal and Performance IQ scores resulted to be statistically different between our three groups. Again the group with ID, alone or in association with ASD or SSD, scored significantly lower than the other two groups, but this time SSD performed slightly worse than ASD, both alone and in co-occurrence with ID.

IQ testing within ASD generally leads to a profile of lower verbal than performance IQ in much of the autistic spectrum, whether high or low functioning (Joseph et al., 2002), but this was not observed across all studies (Siegel et al. 1996; Mayes & Calhoun 2003; Minshew et al. 2005). Our findings are consistent with this minority, probably because of the very high co-occurrence of ID.

Lower verbal IQ is commonly interpreted as a measure of communication and social impairment, which is one of the core symptoms of ASD (Tager-Flusberg & Joseph 2003), but the literature is not really unanimous in this point: beside older evidence of association between smaller IQ divergence (verbal > performance) and better language skills (Lincoln et al. 1998), there are recent studies showing that higher IQ divergences in either direction relate with social symptoms of autism (Black et al. 2009).

For schizophrenia, a recent meta-analysis of 4396 cases with over 745000 controls from 12 independent studies confirmed previous findings on significant decrements in premorbid IQ among future cases, with verbal and non-verbal measures being equally affected (Khandaker et al., 2011). On the contrary a genetic study using data from a large population sample and multiple independent large datasets found schizophrenia polygenic risk score to be associated only with lower performance IQ, as well as polygenic score for performance IQ to be associated with increased risk for schizophrenia. Also lower full IQ resulted to be associated with polygenic risk for schizophrenia (Hubbard et al., 2015).

Some efforts have been made by international research also to characterize the pattern of cognitive functions in ASD and SSD, and certain resemblances have become apparent such as deficits in abstract reasoning and the more complex aspects of memory and language. Ota and colleagues found higher WAIS-R scores in ASD than in schizophrenia suggesting the WAIS score measurement to be an easy and useful method for helping to discriminate between these two groups (Ota et al., 2011). Goldstein and collaborators compared well-diagnosed individuals with high-functioning autism (IQ> or =70) with schizophrenics divided into four subgroups by Ward's method of cluster analysis. The

autism group resembled only one of the schizophrenia clusters, with both showing relatively depressed score on the comprehension subtest among the verbal subtests and a relatively elevated score on block design among the performance subtests (Goldstein et al., 2002).

Our results confirm better WAIS scores in ASD than SSD, also in the co-occurrence with ID, they also suggest for ID to exclude the co-occurrence with SSD and particularly with ASD in the presence of lower scores on verbal and performance IQ.

Also Total IQ mean score were found to be statistically significant different between our three groups. Those with ID, alone or in association with ASD or SSD, scored significantly lower than those with ASD or SSD alone. As for Performance and Verbal IQ scores, the total score was higher in ASD than in SSD, but the trend reversed when these conditions were associated with ID.

As largely expressed in the introduction of this volume, the majority of last years' studies on schizophrenia report patients' premorbid and current total IQ scores to lay in the inferior range (Fioravanti et al., 2012; Bora & Murray, 2014), particularly in people with first-episode and youth-onset (Rajji et al., 2009) and recent theories suggest this cognitive deficit to be the first expression of a complex neurodevelopmental disorder (Reichenberg et al., 2010; Zipursky et al., 2012).

In ASD, the presence of a total IQ impairment is more common than in schizophrenia. Historically, it is estimated at 70% (Volkmar & Pauls, 2003), but recent studies encompassing all the DSM-5 conditions, including DSM-IV-TR Asperger syndrome and pervasive developmental disorder not otherwise specified, suggest that it may be considerably lower (U.S. Developmental Disabilities Monitoring Network Surveillance, 2014).

Khandaker and collaborators have recently reported the total IQ score reduction to partially explain the sequential comorbidity between ASD and SSD. In their study sample 487 (5.9%) children out of 8220 were reported to have ASD at the age of 9 years. Compared with those without ASD showed a lower total IQ and a higher risk of severe psychotic symptoms across years (Khandaker et al., 2014).

Our results confirm better WAIS total scores in ASD than SSD, unless the co-occurence of more severe ID, in which SSD scores are slightly higher than ASD ones. Our findings also confirm very low WAIS total scores to supports the exclusion of co-occurrence of high functioning ASD and, to a lesser extent, SSD. In the case of co-occurrence of ID and ASD the presence of a higher WAIS total score suggests a further co-occurrence of SSD more than ASD.

Study limitations

The present study has some general limitations that must be considered in the interpretation of results. The main one is the small sample size. A study with low statistical power has a reduced chance of detecting true associations and true differences between groups and variables. The consequences of this include overestimates of effect size and low reproducibility of results. The time available to investigate the research problem was pretty much constrained by the due date of our assignment.

Also the number of recruitment centers was constrained and referred to the restricted geographic area of Northwest Tuscany. It is possible that a considerable part of the informants and raters involved in the study have shared some biases in descriptions and score attributions, although the majority of the raters underwent a process of inter-rater reliability for the SPAID tools just before the start of the study.

The study sample is not representative of the population with ID, the percentage of persons with moderate ID is higher than the one reported in the literature, as well as that of persons with severe ID is lower. No persons with profound ID have been included in the sample.

Also the composition of the three groups was quite different. Only 6 out of the 61 study participants were not diagnosed with ID. Participants with ASD were 40, with a gender ratio higher than in the other groups: 28 male and 12 female. Participants with SSD were 28, with a very high prevalence of borderline ID. The number of cases presenting ID in comorbidity with ASD or SSD was 36 and 25, respectively.

However, to our knowledge, this is the largest homogenous collection of data from ID-specific neuropsychological and psychopathological assessment tools referred to adults with ID and co-occurrent ASD or/and SSD.

Furthermore, the SPAID-P and SPAID-DPS, which were included in the assessment battery to assess SSD and ASD in people with ID, had not completed the validation process and could present some validity or reliability issues, although these properties had been preliminary evaluated with good results.

Another limitation is represented by the recruitment method, participants weren't included by randomisation, but by their consecutive referring to the clinical services of our network.

We also regret not have included in the study tools for the assessment of specific cognitive functions tailored for people with ID. They could have helped in explaining the score differences between the co-occurrence of ASD and SSD that emerged for Digit symbol and Block design, as well as for Verbal and Performance IQ.

We hope that these limitations will be revised in future researches.

CHAPTER 5

CONCLUSIONS

The present study allowed to identify some clinical and neuropsychological characteristics that relate most with each of the three specific conditions and their combinations.

Surprisingly, the presence of autistic dimensional characteristics, assessed through the AQ, is not associated with the diagnosis of ASD, particularly with low functioning ASD and ASD co-occurrent with ID, which represent the waste majority of our sample. Instead AQ over threshold scores are associated with the diagnosis of SSD, even if to a low extent.

The lack of empathy, assessed through the EQ, is associated with the diagnoses of both ASD and SSD, although to a higher extent in the latter.

The screening for psychiatric co-occurrence through the SPAID-G revealed higher scores for Simulation in the presence of diagnosis of ID or SSD. Higher scores for DOC and Sexual disorders were found in both ASD and SSD, while Identity disorders, Depression, and Medication side effects are specifically higher in SSD.

More complex statistical elaborations revealed SSD to significantly impact on DOC, Depression, Medication side effects, Simulation, and Identity disorder scores, ASD on Sexual disorder scores, and ID on Eating disorder and Simulation scores. The strong relationship between DOC and SSD, but not ASD, was repeatedly found through different statistical methods.

The comparison of specific behavioural equivalents of psychiatric symptoms, assessed through SPAID-G items, identified higher scores for psychomotor agitation and/or restlessness and unjustified irritation/opposition in all the three diagnostic groups. Aggressiveness, both physical and verbal, toward other people or objects is quite frequent in ID, but not in ASD and SSD. Loss of satisfaction or pleasure for activities or objects, and avoidance or escape from certain objects, people or situations are frequent in ID and SSD groups, but not in ASD group, while indifference or lack of emotions is less frequent in SSD. Arbitrarily attribution of cause-effect links and auditory hallucinations show higher scores in the presence of ASD and SSD diagnoses, but not ID.

For cognitive assessment, through the WAIS, the Block design resulted the less sensitive subtest for diagnosing ID, but it was found to be quite useful in differentiating from ASD and SSD. In fact those with ID alone or in association with ASD or SSD scored significantly lower than those with ASD or SSD alone. The performance was also poorer in ASD than in SSD, both for the conditions themselves and for their association with ID.

Although in a not statistically significant way, ASD score better than SSD on Digit span, Picture completion, Object assembly, and Digit symbol subtests. SSD performs statistically significant better than ASD on the Digit symbol, which expresses visual-spatial, visual-motor integrative, and working memory skills.

Those with ID alone or in association with ASD or SSD also scored significantly lower for Total IQ, as well as for Verbal and Performance indexes.
The Total IQ score was higher in ASD than in SSD, but the trend reverses when these conditions are associated with ID. The Verbal and Performance scores were lower in SSD than in ASD, both for the conditions themselves and for their association with ID.

Table 19. Differences of psychiatric instrumental assessment between ID, ASD, SSD, ASD+ID, and SSD+ID

TOOL	ID	LF*-ASD	SSD	ASD+ID	SSD+ID
AQ	No association (any level of ID)	No association	Association	No association	Association
EQ	No association (any level of ID)	Association	Association ++	Association +	Association ++
SPAID-G areas	Simulation	DOC +, Sexual disorders ++	DOC ++, Simulation +, Sexual, Identity, Depressive disorders, Medication side effects	n.a.	n.a.
SPAID-G items	- psychomotor agitation and/or restlessness +++ - unjustified irritation/opposition +++ - loss of satisfaction or pleasure for activities or objects ++ - avoidance or escape from certain objects, people or situations + - indifference or lack of emotions ++ - aggressiveness, both physical and verbal, toward other people or objects ++	- psychomotor agitation and/or restlessness ++ - unjustified irritation/opposition ++ - indifference or lack of emotions +++	- psychomotor agitation and/or restlessness + - unjustified irritation/opposition + - loss of satisfaction or pleasure for activities or objects ++ - avoidance or escape from certain objects, people or situations ++	- psychomotor agitation and/or restlessness ++ - unjustified irritation/opposition ++ - indifference or lack of emotions +++	- psychomotor agitation and/or restlessness + - unjustified irritation/opposition + - loss of satisfaction or pleasure for activities or objects ++ - avoidance or escape from certain objects, people or situations ++
SPAID-P	No association (any level of ID)	- arbitrarily attribution of cause-effect links +++ - to remain listening position and/or respond to sounds or voices not audible +++	- arbitrarily attribution of cause-effect links +++ - to remain listening position and/or respond to sounds or voices not audible ++	No association	No association

WAIS	block design – verbal IQ - performance IQ - total IQ -	block design --- digit symbol ++ digit span, picture completion, object assembly – verbal IQ ++ performance IQ ++ total IQ ++	block design –- digit symbol + verbal IQ + performance IQ + total IQ +	block design --- verbal IQ - performance IQ - total IQ --	block design -- digit span, picture completion, object assembly -- verbal IQ - - performance IQ - - total IQ -

*LF: Low-Functioning

Our findings usefully integrate the literature indications on clinical factors to distinguish between the three diagnostic groups, and the co-occurrence of ASD and SSD with ID, as summarised in the following table.

Table 20. Clinical Differences between ID, ASD, SSD, ASD+ID, and SSD+ID

	ID	**ASD**	**SSD**	**ASD+ID**	**SSD+ID**
ONSET AND AGE OF RECOGNITION	• Before 18 yrs [most severe ID identified in early years while mild ID may not identified until later (e.g., school entry)]	• Any time post natal but key defining features can be traced back to first three years	• First episode of illness in adolescence or early adult life • "at risk" and prodromal mental states. 25-40% convert • Childhood-onset schizophrenia – rare before 7-8 yrs of age	n.a.	n.a.
CLINICAL FEATURES AND IQ	• IQ <70 • Often physical stigmata • Clinical features associated with functioning level – mild, moderate, severe, profound	• Triad of impairments: social, communication, repeat. behaviours (sensory abnormalities) • Across all functioning levels • Up to 70% have ID	• Positive symptoms • Negative symptoms • Across all levels of IQ but may be premorbid decline in function	see note on WAIS scores	see note on WAIS scores
INTEREST TOWARDS OTHERS	variable from case to case	unusually disinterested in shared sense and others' thought	try to guess other's attribution of sense	n.a.	n.a.
DELUSIONS	not present	not present (but fantastic thought)	present	not present (but fantastic thought)	present (for severe ID as a behavioural equivalent)
HALLUCINATIONS	not present	not present (but sensory abnormalities)	present	not present (but behaviours with confounding effect)	present (for severe ID as a behavioural equivalent)
ANATOMICAL ANOMALIES OF THE CNS	variable from case to case	diffused gray matter increase and anomalies in the neuroanatomical networks	enlarged ventricular spaces and hypofrontality	n.a.	n.a.
PSYCHIATRIC COMORBIDITY	Psychopathology frequent: estimated to be X4 that of the general population	Asperger: mood and anxiety disorders common Autism with ID compared to ID only: • Greater frequency of new onset (episodic) disorders e.g., mood, anxiety, adjustment disorders • Greater frequency of background (non episodic) disorders e.g., ADHD, tics, phobias • Episodic and non episodic disorders co-exist	More recently the focus of research attention (e.g., depression, anxiety)	No association	Association

AQ	No association (any level of ID)	No association	Association	No association	Association
EQ **SPAID-G areas**	No association (any level of ID) Simulation	Association DOC +, Sexual disorders ++	Association ++ DOC ++, Simulation +, Sexual, Identity, Depressive disorders, Medication side effects	Association + n.a.	Association ++ n.a.
SPAID-G items	• psychomotor agitation and/or restlessness +++ • unjustified irritation/opposition +++ • loss of satisfaction or pleasure for activities or objects ++ • avoidance or escape from certain objects, people or situations + • indifference or lack of emotions ++ • aggressiveness, both physical and verbal, toward other people or objects ++	• psychomotor agitation and/or restlessness ++ • unjustified irritation/opposition ++ • indifference or lack of emotions +++	• psychomotor agitation and/or restlessness + • unjustified irritation/opposition + • loss of satisfaction or pleasure for activities or objects ++ • avoidance or escape from certain objects, people or situations ++	• psychomotor agitation and/or restlessness ++ • unjustified irritation/opposition ++ • indifference or lack of emotions +++	• psychomotor agitation and/or restlessness + • unjustified irritation/opposition + • loss of satisfaction or pleasure for activities or objects ++ • avoidance or escape from certain objects, people or situations ++
SPAID-P	No association (any level of ID)	• arbitrarily attribution of cause-effect links +++ • to remain listening position and/or respond to sounds or voices not audible +++	• arbitrarily attribution of cause-effect links +++ • to remain listening position and/or respond to sounds or voices not audible ++	No association	No association
WAIS	• block design – • verbal IQ - • performance IQ - • total IQ -	• block design --- • digit symbol ++ • digit span, picture completion, object assembly – • verbal IQ ++ • performance IQ ++ • total IQ ++	• block design –- • digit symbol + • verbal IQ + • performance IQ + • total IQ +	• block design --- • verbal IQ - • performance IQ - • total IQ --	• block design -- • digit span, picture completion, object assembly -- • verbal IQ - - • performance IQ - - • total IQ -

Moreover, study results indicate that the use of tools and diagnostic criteria specific for ID considerably increases the diagnostic sensitivity for ASD, SSD and other co-occurrent psychiatric disorders.

We hope that these findings might contribute to further research aimed at defining better criteria of differential diagnosis and comorbidity between ID, ASD, and SSD.

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