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Depressive and Bipolar Disorders in persons with Intellectual Disability and low-functioning Autism Spectrum Disorder.
The development and first validation of a new diagnostic tool (SPADD-M)

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LIST OF ABBREVIATIONS

IDD	Intellectual developmental disorder
ID	Intellectual disability
BIF	Borderline Intellectual Functioning
ASD	Autism Spectrum Disorder
LF-ASD	Low-functioning Autism Spectrum Disorder
MDs	Mood Disorders
DDs	Depressive Disorders
BDs	Bipolar Disorders
MDD	Major Depressive Disorder
PDD	Persistent Depressive Disorder
PD	Psychiatric Disorder
PBs	Problem Behaviors
ICD	International Classification of Disorders
DSM	Diagnostic and Statistical Manual for Mental Disorders
SPAIDD	Systematic Psychopathological Assessment for persons with Intellectual and Developmental Disabilities
NDs	Neurodevelopmental Disorders
SSDs	Schizophrenia Spectrum Disorders
GAD	Generalized Anxiety Disorder
OCD	Obsessive-Compulsive Disorder
ICD	Impulse Control Disorders
ODD	Oppositional Defiant Disorder
ADHD	Attention Deficit/Hyperactivity Disorder
EDs	Eating Disorders
BED	Binge Eating Disorders
SSRIs	Selective Serotonin Reuptake inhibitors
TCA	Tricyclic Antidepressants
FGA	First Generation Antipsychotics
SGA	Second Generation Antipsychotics
BDZ	Benzodiazepines
AD	Antidepressants
AP	Antipsychotics

SUMMARY

Background: Current literature reports the frequent co-occurrence of psychiatric disorders (PDs) in adults with Intellectual and Developmental Disorders (IDD), such as Intellectual Disability (ID) and Low-Functioning Autism Spectrum Disorder (LF-ASD). Unfortunately, the adaptations of diagnostic criteria for PDs as well as the standardization of the psychiatric diagnostic process in this population still represent an unmet need, with relevant implications for both the management of mental health issues and the research in this field. In fact, the assessment of PDs in people with IDD requires appropriate modifications in respect to the general population, to adjust for cognitive dysfunctions, language and communication limitations, sensory impairments, skill deficits, impairment of adaptive behavior, and physical disabilities. Moreover, research and clinical experience highlight the interpretation of problem behaviors (PBs) to interfere with the psychiatric diagnostic process. Among PDs, depressive and bipolar disorders (DDs and BDs, respectively), seem to be very common and associated to a variety of behavioral, medical and treatment issues in these populations. Indeed, the prevalence rates of DDs and BDs in large ID population-based studies are estimated to be about 5% and 2.5%, respectively. The prevalence rates are at least doubled in the overall ASD population and even higher rates can be found in clinical studies. These data indicate the co-occurrence of mood disorders (MDs) in intellectually disabled persons to be a relevant clinical issue, but some difficulties may arise as far as a certain number of patients, mostly those with lower cognitive and adaptive functioning, have atypical presentations. To implement the validity of clinical diagnosis and in order to operationalize the adaptations and descriptions of MDs in ID, the design and experimentation of specifically addressed assessing tools is required.

Aim: The main objective of the present study was to develop and to validate the version for DDs and BDs of the Systematic Psychopathological Assessment for persons with Intellectual and Developmental Disabilities (SPAIDD-M). Secondary aims of the present study were the investigation of the prevalence and clinical features of MDs in people with ID and LF-ASD, including demographic, anamnestic, familial, and clinical variables as well as the course and clinical specificities of MDs in this population.

Method: 233 adults with ID and with an eventual co-occurrence of ASD, aged 16-65 years, were recruited among those attending the residential and clinic-rehabilitative facilities of the San Sebastiano Foundation in Florence and of the wide network of the Research and Clinical Center (CREA). The sample underwent a complex anamnestic evaluation implying the collection of demographics, psychosocial, familial, medical and psychiatric information via a semi-structured interview developed ad hoc. The SPAIDD-M 1.2 was completed for all the participants. For the evaluation of concurrent validity, 197 participants (85.3%) were administered with the Diagnostic Assessment for the Severely Handicapped (DASH-II), and 141 (68.4%) were assessed with DSM-5 criteria for Major Depressive Episode, Mania and Hypomania, adapted according to the definition of DM-ID-2. Mixed features of major depressive episode (MDE) and (hypo)manic episode were evaluated in 110 probands. The overall sample was stratified based on ID severity as described by the following three groups: 1. Borderline intellectual functioning (BIF) and mild ID; 2. Moderate ID; 3. Severe and profound ID. The test-retest reliability was evaluated in reference to three study participants (one for each ID level) through

the administration of the tool to the same informants at baseline and after two-to-three months. The inter-rater reliability was evaluated through a special session which included eight different professionals rating for the same study participant. χ^2 for categorical variables, ANOVA and F-variance for continuous variables tests were used for comparisons between groups. The psychometric properties evaluated were: internal consistency, inter-rater reliability, face validity, criterion validity, test-retest reliability, concurrent validity. To explain the variance, a factorial analysis was performed. For other clinical variables, stepwise backward procedure logistic regression models were elaborated.

Results: SPAIDD-M 1.2 showed good psychometric properties. The face validity, which underwent two revisions, resulted to be comprehensible for most evaluators. Some difficulties remained about the completion of the items relative to mixed features. The internal consistency was very good, with a Cronbach's α of .937, as well as an acceptable inter-rater reliability expressed by a Cohen's K coefficient ranging from .870 to .575. Criterion validity was also good for both the major depressive and the (hypo)manic episodes. The concurrent validity was found to be high with moderate correlations between SPAIDD-M and DASH-II scores, and strong correlations between SPAIDD-M and DSM-5 diagnoses. A factor analysis identified four main factors explaining about the 38% of the score variance. The sample was very homogeneous regarding all the demographic, socio-economic, familial, medical and psychiatric variables explored. The comparisons of the psychiatric diagnoses indicated the rates of MDs to be equally distributed across the three ID groups, whereas this homogeneity was not evident before the assessment provided in the study protocol. Indeed, before the study, the severe/profound group had been correctly diagnosed only in the half of the cases as well as other participants in the other groups had to be diagnostically reviewed. In our sample, MDs were associated to a higher number of mental health issues in the personal and family history as well as a higher use of psychotropics. LF-ASD resulted to be at higher risk for MDs, mostly BD type I, and the affective illness was more frequently associated to catatonia, mixed features and rapid cycling. The analyses of differences between DDs and BDs as presented in ID did not identify any statistically significant feature, and both clinical conditions resulted to be equally associated to high rates of psychotic, catatonic and mixed symptoms in a more frequent way than it is reported in the general population. The diagnosis of BD was associated to a complex pattern of comorbidities including ADHD, impulse control disorders, binge eating and the presence of a familial psychiatric burden. By the contrary, DDs were associated to anxiety disorders and family history of ASD.

Limitations of the study: Sample size, selection, referral and recall biases. Concerns regarding the use of behavioral equivalence. Difficulties in the differential diagnosis with other psychiatric and iatrogenic conditions beyond DDs and BDs.

Conclusions: The study provides preliminary information regarding the psychometric properties and the effectiveness of specifically addressed assessment in the ID and LF-ASD population. The prevalence data are not generalizable to the overall ID population. Some clinical information has been drawn regarding the peculiar presentations of MDs in persons with ID pointing towards a pathoplastic effect of the basal

neurodevelopmental condition. Further research is needed to operationalize the assessment of DDs and BDs in ID and LF-ASD.

CHAPTER 1

1.1 INTRODUCTION TO THE ISSUE

In the last decades, the interest towards psychopathology of Intellectual Disability (ID) and Autism Spectrum Disorder (ASD) has significantly raised within the neuroscientific community, although research activity and clinical advances have been limited. One of the most urgent need is to overcome significant gaps in the identification of psychiatric disorders (PDs) in ID and ASD people with severe cognitive and communication impairment in order to develop reliable and evidence-based guidelines for management strategies and psychopharmacological treatments.

Diagnosing PDs in persons with ID (PwID) constitutes a challenge from different points of view, including the fact that the diagnosis is generally made starting from the psychopathological knowledge derived from the general population, upon which neuroscientists have been debating for the last 50 years. Until the 1980s, there was a generalized belief that PwID could not suffer from mental health issues and all the eventually thought, speech, mood, psychomotor, perceptual and behavioral abnormalities were somehow attributed to the neurodevelopmental condition. There are memories of my oldest colleagues remembering their oldest colleagues saying “well, he’s oligophrenic, what else?”. Similar considerations were made upon people with ASD, especially those with low-functioning ASD (LF-ASD) or co-occurring ID, with few studies focusing only on developmental age. Afterwards, some pioneer clinicians claimed that PwID and LF-ASD may present the full range of PDs, and a body of literature was produced in support to this view (Moss and Goldberg, 1991, Sovner and Hurley, 1982, Sovner and Hurley, 1983).

Significant problems are intrinsic to the psychiatric diagnostic process in ID and LF-ASD people, and most of them remain not completely solved (Bertelli et al., 2012, Bertelli, 2015, Underwood et al., 2015). In fact, in PwID and LF-ASD psychiatric manifestations may be difficult to detect and correctly framed according to the currently used standardized categorical diagnostic systems that have been designed for people with typical neurodevelopment. This problem is directly proportional to the increasing severity of cognitive, communicative and language impairment. As a fact, subjects with a restricted behavioral and communicative repertoire may express any kind of distress through a limited span of manifestations. A strong effort is needed to interpret these manifestations and to find time after time the correct solution among a broad range of etiological issues. Transient behavioral abnormalities might be the main or most evident expression of distress, including reactions to incident physical problems, pain, environmental stressors, psychological needs but also co-occurring PDs. Moreover, it is not a secondary aspect that the research on genetic syndromes associated to ID demonstrated that specific behavioral disturbances and/or psychiatric manifestations are related to a variety of complex interactions between environment and specific neurobiological underpinnings (Tunnicliffe and Oliver, 2011). This may imply that the same behavior (e.g. self-injury) may be related to different biological, psychological and behavioral mechanisms which may require differentiated approaches. Unfortunately, the attitude of care-givers and professionals frequently consists of applying urgency-based strategies rather than a

scientific, evidence- and observation-based approach. The final effect is a widespread inequal access to optimal sanitary and psychological care for people with ID and LF-ASD.

A vicious circle affects advances in research. The peculiar presentations of PDs in PwID and LF-ASD raise perplexities about the full applicability of standardized diagnostic criteria, thus in the last years the scientific community have made significant efforts to provide adaptations to those criteria encompassing a broad range of behavioral and atypical manifestations commonly associated to specific PDs in this population. By the contrary, some researchers tried to develop independent criteria specifically designed for PwID. The lack of a unitary perspective inevitably lowered the quality of most research: population-based studies accounting for official administrative records usually failed to detect the actual prevalence and features of PDs because of the poor sensitivity of standardized criteria. Otherwise, the clinical research often omitted to clarify the criteria applied for the diagnosis of both PDs and ID with the final result of interesting but often poorly generalizable data and, sometimes, overestimation of psychiatric comorbidity. These issues are also strictly connected with the substantial lack of reliable assessing instruments, to support the clinicians in this complex diagnostic process and to allow full generalizability of research results regardless the level of ID.

Affective Disorders are highly prevalent in PwID and LF-ASD, although data derived from epidemiological and clinical studies vary with a very broad range of prevalence. This disparity may be due to significant differences across studies in the methodology and the clinical definitions used to make the diagnoses. The co-occurrence of Mood Disorders (MDs) has several implications. From a clinical point of view, it is associated with both a significant worsening in cognitive and pragmatic functioning as well as with a substantial reduction of the functional and health-related outcomes comparing to the expected potential of the individual. Noteworthy, especially in subjects with substantial cognitive, communicative and language deficits, both mania and depression are significantly associated to challenging behaviors, such as increased stereotypic behavior and movements, oppositional-defiant behaviors, aggressiveness, self-injury (Matson and Smiroldo, 1997, Matson et al., 1999). Such behavioral abnormalities may become prominent in the clinical picture and shadow other symptoms, which are clearly referable to MDs. For example, restlessness, temper tantrums, defiant behavior and aggression are counterintuitively common in PwID during depression and, at first sight, it can be difficult to draw the correct conclusion. Unfortunately, inappropriate psychopharmacological interventions, whose administration is frequently based on the urgency to suppress abnormal and challenging behaviors, often exert further diagnostic difficulties. A diagnosis based on the cross-sectional observation can be particularly misleading as the main characteristic of MDs consists in cyclicity and recurrent course.

Although it is generally accepted that in PwID and LF-ASD depression and mania may present with atypical and peculiar features, especially in persons with lower cognitive and communication skills, there is no full agreement regarding which symptoms, behaviors and course features actually characterize depressive and bipolar disorders in this heterogeneous population. Beside the diagnostic issues shared with the other PDs in PwID and LF-ASD, MDs show specific issues that are quite common in clinical practice but poorly explored, such as the differential diagnosis from medication side effects or negative symptoms of schizophrenia, the distinction between mania and hypomania, the differential diagnosis between bipolar disorder and

schizophrenia spectrum disorders mostly in the presence or suspect of psychotic symptoms, and the identification of mixed and rapid cycling features.

In this perspective, advances in the diagnostic procedure of MDs are needed as an essential starting point for the improvement of the research regarding interventions and equity to the access to optimal treatments. Current standardized diagnostic manuals, namely the International Classification of Disorders (ICD) of the World Health Organization and the Diagnostic and Statistical Manual for Mental Disorders (DSM) of the American Psychiatric Association, have been used as basis for manuals providing the adaptations of PDs to ID and LF-ASD. The adaptations for MDs mainly consist in offering a variety of descriptions and examples to encompass the range of atypical symptoms and behaviors that have been associated in the literature to depression and mania. However, given the limitations of most studies in this field, further research is needed to produce proper standardized diagnostic criteria. In this desirable advancement, the development of valid assessing instruments may play a central role.

The present study focuses on the development and first validation of a diagnostic tool for depressive and bipolar disorders as they are described in the fifth edition of the DSM. The instrument is part of a battery named Systematic Psychopathological Assessment for persons with Intellectual and Developmental Disabilities (SPAIDD), whose projecting was started in Italy 16 years ago (Bertelli et al., 2003, Bertelli et al., 2012) with the aim of providing clinicians and other professionals working with ID/LF-ASD with a comprehensive set of tools to be used for all the different phases of the clinical intervention, such as the diagnostic screening, the diagnostic refinement, and the symptoms follow-up. All the tools belonging to the SPAIDD system can be used across the range of ID, but they have been designed for people with important communication and cognitive impairment. In fact, they include lists of observable symptoms (mainly behaviors) to be checked for presence or absence through an interview to a significant proxy. Nonetheless, the PwID can be involved in the assessment when able to integrate the information. The aim of this study was to evaluate the psychometric properties of the version for MDs of the SPAIDD (SPAIDD-M), but also to show preliminary results about the prevalence and presentation of depressive and bipolar disorders in PwID.

1.2 INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

1.2.1 DEFINITION AND DIAGNOSTIC CRITERIA

The conceptualization of ID is controversial as it cannot be considered a disease but a complex and heterogeneous group of conditions characterized by deficit in cognitive functioning prior to the acquisition of abilities through learning (Salvador-Carulla and Bertelli, 2008). A disruption of typical neurodevelopment with various degree of functional alterations and/or structural abnormalities of the Central Nervous System (CNS) underlies the conditions falling under the label of ID. They can be related or caused by a variety of etiopathological factors that in half of the cases are not identifiable. As ID involves the neurodevelopment, it occurs early in life and has to be considered a life-long condition and deficits in intellectual functioning tend to remain stable ((APA), 2000), while improvements in adaptive behavior can occur ((APA), 2013). The final presentation of the individual clinical picture may include differential impairments of intelligence, learning, language and communication, adaptive behaviors, and abilities.

Before the early nineteenth century the terms used to label intellectually disabled persons included idiocy, deficiency, oligophrenia, mental deficiency, mental handicap, mental sub-normality etc (Schalock et al., 2007). The term *mental retardation* (MR) has been the label of diagnostic categorical systems used until now (ICD-10 and DSM-IV-TR) even if in the last decade the research community, professionals of this field and disability rights movements made an attempt to replace it with other terms with the double purpose of removing negative connotations and stigma and to stress that ID belongs to neurodevelopmental disorders. Indeed, both ICD and DSM in their latest versions (ICD-11 and DSM-5) completely abandoned MR and chose *intellectual disability* or *intellectual developmental disorder* (IDD) ((APA), 2013, (WHO), 2018). Comparing to the label MR, ID refers to a significant reduction of global and/or specific abilities to achieve certain targets considered appropriate for average IQ persons. More specifically, the words ID refer to intelligence and in particular to a deficit of the logical-deductive process with a reduced ability to learn new skills with consequent impairments of adaptive functioning, in line with current definition of intelligence (Bertelli et al., 2014).

The history of the terminology is not merely a matter of words but represents the reflex of the evolution of different perspectives and conceptualizations. Differences have been supported by changes both in sociocultural and health policies frameworks, as well as the ever-expanding advances in the knowledge of neurobiological and genetic bases and causes of ID that dramatically changed the way we currently look at ID (Girimaji and Pradeep, 2018). Some ambiguities are summarized by the position of MR in the different editions of the DSM. Both the DSM ((APA), 1952)and II ((APA), 1968) included MR in a section separated from other psychiatric diagnoses. The DSM III ((APA), 1980) moved MR in the Axis I, among the disorders with onset usually occurring in childhood and adolescence. Then the DSM III-R ((APA), 1987) and DSM IV ((APA), 1994) moved RM back on Axis II along with the personality disorders and pervasive developmental disorders (PDD), or just with personality disorders, respectively. The above-mentioned repositioning movements reflected uncertainties regarding the nature of ID as health condition or disability, but also regarding the concept of ID with respect to psychiatric disorders: the concept that intellectually disabled persons may suffer from mental health illness equally to the general population is relatively new and before

the last four decades most researchers claimed that a co-occurrence would not be possible (Earl, 1961). Finally, IDD has moved back again in Axis I with acceptance of the concept of dual diagnosis; this change created the prerequisite to the implementation of adapted criteria for PD in this population.

In the DSM-IV-TR and ICD-10 ((APA), 2000, (WHO), 2010), the key feature of MR was a general intellectual functioning impairment qualified by an IQ significantly below the average (criterion A). Significant limitations in adaptive functioning areas had to be present in at least two of the following performance domains: 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 be 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). Significant subaverage general intellectual functioning is defined by the APA ((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).

In the DSM-5 ((APA), 2013) the term MR was officially replaced by ID or IDD then adopted by the ICD-11 ((WHO), 2018), highlighting the convergence between the two classificatory systems.

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, mostly in order to recalibrate the severity and, subsequently, the supports needed.

In the DSM-5, the specific age limit of 18 years 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). This modification as well as the inclusion of ID in the first chapter of DSM-5 encompassing all the neurodevelopmental disorders represents one of the major advances of the new classification, indicating that ID is nowadays considered as the outcome of pathophysiological mechanisms affecting the developing brain and influencing its functioning along the entire life-span (Girimaji and Pradeep, 2018).

The subaverage general intellectual functioning (Criterion A) is defined by an IQ score of approximately two standard deviations or more below the mean of the general population. When extremely low (under 60), IQ measures are no longer valid. This concept found a form in the ICD-11 definition of IDD as "a group of etiologically diverse conditions originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behavior that are approximately two or more standard deviations (SDs) below the mean (approximately <2.3rd percentile), based on appropriately normed, individually administered standardized tests. Where appropriately normed and standardized tests are not available, diagnosis of DID requires greater reliance on clinical judgment based on appropriate assessment of comparable behavioral indicators" ((WHO), 2018). 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.

The term adaptive behavior 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 ((WHO), 2018, (WHO) and 2017, Schalock et al., 2010).

Both DSM-5 and ICD-11 agreed that the definition of the severity levels had to rely more on adaptive functioning than on IQ scores, since the adaptive functioning in the areas of conceptualization, socialization, and practical skills determines 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 emphasis given to specific, peculiar and sometimes parcel deficits represents a further opening toward a new conceptualization of intelligence and its disorders, indicating research perspective for the next future: 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 underlying etiopathogenetic factors (Bertelli et al., 2014). For example, subjects 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). Different cognitive profiles are related to the differential involvement of specific neurotransmitters and neuroanatomical circuits: differences may have impact on behavioral phenotypes (Tunnicliffe and Oliver, 2011), adaptive profiles and, possibly, specific vulnerability to PD. Going fast forward, it is also possible that specific dysfunctions of some neural circuitries may imply different responses to psychopharmacological treatments: the implications for management strategies and outcome estimation are very intriguing.

In summary, the new approach gives more relevance to various behavioral and clinical indicators in supplementing, complementing or substituting formal IQ scores in diagnosing ID and quantifying the severity level (Girimaji and Pradeep, 2018). Some differences between the two classificatory systems regard the emphasis given to the components of the diagnostic process. ICD-11 substantially equalizes intellectual functioning and adaptive skills in specifying the severity of IDD by means of comprehensive descriptions of behavior and impaired abilities associated to each degree of ID. This expedient is functional to broaden the possibility of clinical diagnosis not fully supported by standardized testing, often not available or not practically and routinely used in low- and middle-income countries (Girimaji and Pradeep, 2018). This approach looks also forward to research and administrative utility of diagnostic criteria. On the other hand, DSM-5 puts in first sight pragmatic requirements: determining ID level only through the quantification of adaptive functioning, especially in lower ranges of IQ, where the measure is less valid.

Both classifications maintained the four levels of ID: mild, moderate, severe and profound. In ICD-11 the subcategory "provisional subtype" was added, whereas DSM-5 included global developmental delay (GDD) and unspecified IDD. The provisional subtype indicates the presence of some kind of disorder of intellectual development but the evaluation cannot be considered conclusive because the very early stage of the individual's development (infants and children before the age of 4) or the assessment of functioning and adaptive behavior is not valid for a variety of reasons (sensory disabilities, severe locomotor impairment, severe problem behaviors or co-occurring mental and behavioral disorders (Rutter et al., 1975). GDD encompasses only cases of developmental delay in individuals below the age of 5 not able to participate to assessments ((APA), 2013), whereas other peculiar cases can be included into the unspecified subcategory.

ICD-11 also mentioned BIF, defined as a reduction of mean scores in standardized assessments of intellectual and adaptive functioning of 1-2 SD comparing to the average IQ. ICD-11 does not consider BIF as a diagnosable disorder but as a "condition of interest". Indeed, the growing body of literature on BIF indicates on one hand the need of early interventions for this condition ((APA), 2013), and on the other hand the high prevalence of BIF among certain psychiatric populations and, by the contrary, the higher vulnerability of persons with BIF to develop psychiatric disorders, addiction, social, employment and legal problems across the lifespan (Deb et al., 2001a, Hassiotis, 2015). DSM-5 placed BIF in the section III, "Other Conditions that

may be a Focus of Clinical Attention," under the subsection "Other Circumstances of Personal History", not specifying diagnostic criteria for BIF. The DSM-5 code for BIF must be used when the condition may impact the clinical presentation, treatment and outcome of other diagnosable disorders.

The debate on ID classification could have serious implications. Diagnostic categories are used throughout the world to specify the type of population eligible for specific health care, educational and social services. Therefore, the location of ID as *disability* or *health condition* has the potential of impacting health statistics, health policy, and the services available for this vulnerable population (Salvador-Carulla et al., 2011). ICD-11 took a balanced position on this debate clearly conceptualizing ID as a health condition or a disorder rather than merely a disability: the basic condition may lead to various degrees of disability that can be evaluated and measured under the International Classification of Functioning Disability and Health (ICF).

1.2.2 EPIDEMIOLOGY

The prevalence of ID is estimated between 1 and 3%, and the incidence is estimated to be around 1.8% (Harris, 2006, Heikura et al., 2003). 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).

The prevalence of BIF is estimated between 12.3%; for example Hassiotis et al. (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 females in both adults, children/adolescents. Among adults, the male-to-female ratio varies 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 offer of health services and the unmet needs of intellectually-disabled people has become incalculable ((WHO), 2007).

1.2.3 ETIOPATHOGENESIS

IDs can result fromaa different combination of specific causative factors, both of genetic and environmental origin (Bertelli and Kishore, 2014). Historically, people with ID have been classified in two broad categories on the base of the etiology of ID. In the first category, accounting for about the half of the IDs, an organic insult is identifiable as the probable cause of delayed cognitive and emotional development. In this group are included those subjects with perinatal asphyxia or hypoxia or other pre-perinatal insults as in the case of cerebral palsy, documented substance/medication use during pregnancy, pre-, peri- or post-natal exposure to infections or toxins, but also genetically-based conditions as chromosomopathies, metabolic disorders, tuberosclerosis and neurofibromatosis. The second category is constituted by those subjects without an

identified cause of ID, at least according to current knowledge and available diagnostic procedures. The cause is unknown for up to 60% of cases (Rauch et al., 2006). It has been suggested that this group would include most people with mild ID (Volkmar et al., 2007).

A. Prenatal causes

Genetic factors

Conventionally, genetic-related IDs are dividend in syndromic and non-syndromic forms: syndromic forms are characterized by specific constellations of clinical, radiological, metabolic or biological features. In non-syndromic forms the cognitive impairment is the only manifestation of the disease. This distinction has been and continues to be useful in clinical approach; however, giving the never-ending expansion of knowledge in genetics and neurobiology, some forms previously considered non-syndromic are nowadays recognized as syndromic (Durkin, 2002, Frints et al., 2002, Ropers and Hamel, 2005). Current literature reports variable rates depending on the type of sampling: non syndromic ID is estimated around 30%-50% of the cases (Daily et al., 2000), whereas a genetic disorder is identifiable with rates ranging from 17% to 50 (Rauch et al., 2006, Moeschler et al., 2006, Kaufman et al., 2010).

More than a thousand of genes are involved in the etiopathogenesis of ID and more than 290 genes have been associated with specific clinical phenotypes, metabolic, and neurological disorders causing ID (Chelly et al., 2006, Kahler and Fahey, 2003, Levy, 2009). Trisomy 21 is the chromosomopathy responsible for over 95% of Down's syndrome, which is the best-known genetic cause of ID (Patterson and Costa, 2005, Rauch et al., 2006). Other relatively frequent genetic conditions include Fragile X syndrome (Leonard and Wen, 2002), Turner syndrome, Klinefelter's syndrome (Money, 1993), neurofibromatosis (or von Recklinghausen's disease), phenylketonuria, Williams's syndrome, and Prader-Willi syndrome. ID can occur in other genetic syndromes like tuberous sclerosis, Huntington's disease (Mouridsen and Sorensen, 1995, Raznahan et al., 2007), mucopolysaccharidosis, alcaptonuria, and porphyria (Kahler and Fahey, 2003, Levy, 2009).

Consanguineous marriage produces a 5-fold increase of the risk of transmission and expression of genetic conditions associated to recessive genes (Ten Kate, 2012).

Rare *de novo* point mutations, for example copy number variants (CNV) mutations, are related to an increasing amount of cases of Idiopathic ID (de Ligt et al., 2012). Microarray studies, and exome sequencing techniques found CNVs in approximately 15% of PwID (Ropers and Hamel, 2005, Pfundt and Veltman, 2012).

Studies reported 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., 2010, Morrow, 2010).

For example, Berkel and colleagues (Berkel et al., 2010) found 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 (Berkel et al., 2010, Cook and Scherer, 2008, Fernandez et al., 2010), while deletions of the 1q21.1 region were detected also in schizophrenia (International Schizophrenia, 2008).

Epigenetic mechanisms

Epigenetic regulation has been implicated in the causation of several forms of ID: in some cases, gene imprinting may cause different phenotypes and syndromes as in the case, for example of Prader-Willi and Angelman syndromes, Silver–Russell syndrome and Beckwith–Wiedemann syndrome¸ Smith–Magenis syndrome and Potocki–Lupski syndrome (Badcock, 2011). According to the theory of the imprinted brain, the predominant expression of maternal or paternal genes in some specific chromosomal regions may cause functional imbalance. Some authors observed that the maternal/paternal imprinting of a mutated gene may cause clinical pictures and phenotypes with opposite features (Badcock, 2011). A similar mechanism has been hypothesized in the etiopathogenesis of some autistic forms, according to the idea that autism may represent a paternal bias in the expression of imprinted genes (Baron-Cohen, 2002).

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 forms (Dragich et al., 2000, Gibbons et al., 2009, Nan et al., 2007, Sanchez-Mut et al., 2012).

In most cases, modifications in the expression of genes can be related to environmental factors before and after birth *via* epigenetic mechanisms (Zahir and 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 and 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 twelfth month of age.

Exposure to pollutants, heavy metals, and harmful medications such as thalidomide, phenytoin and warfarin in early pregnancy, to substances of addiction such as alcohol, nicotine and cocaine can also cause delays in the development or ID (Behnke et al., 2013, Daily et al., 2000, Ke and Liu, 2012, Sithisarn et al., 2012).

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

B. Perinatal causes

Perinatal causes include complications in delivery, severe prematurity, very low birth weight, birth asphyxia or hypoxia, and birth trauma. Furthermore, neonatal complications in the first 4 weeks of life including septicaemia, severe jaundice, and hypoglycaemia may severely impact the following development of the SNC (Nosarti et al., 2004, Kolevzon et al., 2007). The measure of this impact and its manifestations across the life-span are not limited to ID, which may be considered one pole of the continuum including other neurodevelopmental conditions and several psychiatric disorders (i.e. ASD, ADHD, bipolar disorder and schizophrenia) (Owen, 2012, Owen and O'Donovan, 2017).

Low birth weight at delivery can be due to genetic causes as well as environmental factors encompassing poor nutritional contribution in uterus associated with placental insufficiency, or others damaging agents. Low-weighting children for gestational age show retardation in foetal growth and subsequent neurological complications that are different from 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 the degree of maturity and birth weight (<1500 grams) (Winter et al., 2002, Marlow et al., 2005). Low-weight at birth may also be caused by malnutrition. Recently, the issue of diet during pregnancy arose interest even in Western countries given the increasing percentages of vegetarian and vegan diet regimens among women, also during pregnancy and during breast-feeding. A vegan diet seems to be associated to lower birth weight comparing to vegetarians and omnivorous mothers (Ferrara et al., 2019). Long-term follow-up are lacking in this field to draw conclusions. Structural abnormalities of the CNS are more common among children born at lower limit of viability and weight, while learning disabilities affect more frequently children of lower socioeconomic status. This finding supports the idea of a further contribution of adverse childhood events to cognitive performance (Ritchie et al., 2011).

C. Postnatal causes

During the postnatal period, which includes infancy and childhood, brain infections such as encephalitis, and bacterial meningitis are observed as causes of variable degrees of CNS maturation disruption (Noyola et al., 2001). Furthermore, encephalic traumatism, severe and prolonged malnutrition can lead to some kind of ID (Anderson et al., 2005, Leonard and Wen, 2002). 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 (Emerson and Hatton, 2007, Leonard and Wen, 2002).

Neuroanatomical abnormalities

Structural abnormalities of the CNS are the result of a multitude of insults that are primarily of prenatal origin. Primary malformations including neural tube defects, cerebral dysgenesis, and congenital hydrocephaly or hydranencephaly can be associated with moderate to profound ID.

PwID may show a variety of damages in the integrity of the brain's structures (McDaniel, 2005, Plomin and Kosslyn, 2001). There are no alterations univocally associated to ID, on the contrary it is not uncommon to find no macroscopic SNC alterations in PwID.

Cortical grey matter volumes are related to the integrity of circuitries involved in several executive functions such as planning, working memory, and attention. Several studies found negative correlations between low IQ and reduced total volume of the frontal grey matter (Reiss et al., 1996, Sowell et al., 2001), particularly in the orbitofrontal and medial frontal regions (Frangou et al., 2004).

Moreover, white matter tracts including the corpus callosum, cingulum, uncinate fasciculus, corticospinal tract and optic radiation, may be damaged in people with ID (Yu et al., 2008).

The corpus callosum, connecting the right and left cerebral hemispheres, has been indicated by some studies as a vulnerable structure in ID: some studies found thinned or reduced size of the corpus callosum, particularly in anterior subregions (Njiokiktjien et al., 1994, Spencer et al., 2005). The thinning of the corpus callosum may be associated to impairments of sustained attention and adaptive skills during complex cognitive tasks (Colom et al., 2006). Other important structures possibly involved in the pathophysiology of IDs are the cingulum, uncinate fasciculus, and corticospinal traits. A significant left-greater-than-right asymmetry of the cingulum seems associated with impairment of executive functioning (Gong et al., 2005). Abnormalities of the uncinate fasciculus are related with deficits in verbal, visual memory, and executive performances (Levine et al., 1998), while the corticospinal tract plays a role in the control of discrete finger movements (Martin, 2005).

Sensory impairment in PwID are not infrequent. For example, optic radiation or geniculo-calcarine tract alterations are associated in PwID with visual impairments (Warburg, 2001), strabismus, loss of visual acuity, and amblyopia (Atkinson et al., 2001).

1.2.4 PROBLEMS ASSOCIATED WITH INTELLECTUAL DISABILITY (INTELLECTUAL DEVELOPMENTAL DISORDER)

Medical illnesses

PwID may present a wide range of co-occurring pathologies with higher rates than the general population (Kwok and Cheung, 2007). The most frequent disorders are: epilepsy, gastro-oesophageal reflux disorder (GORD), constipation, visual impairments, hearing impairments, osteoporosis, respiratory infections, risk of aspiration and choking, and repeated accidents or falls. Diabetes is diagnosed in PwID more than twice 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 such 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 and Janicki, 2008).

Epilepsy is one of the most common chronic illnesses diagnosed in PwID, both in syndromic as in idiopathic forms. Shared neurobiological underpinnings are suspected in most cases. Associated problems include global skill deficits, wetting, soiling, walking problems, attention seeking, lack of empathy and mood swings (McGrother et al., 2006). Epilepsy and significant EEG alterations are common in ASD too (Mathewson et al., 2012). The management of epilepsy in ID presents several issues and requires a holistic approach. In fact, psychiatric symptoms and communication impairment often complicate the diagnosis, as well as higher rates of resistance to usual anticonvulsant treatment regimens (McGrother et al., 2006). By the contrary, epilepsy and its treatment may negatively impact physical, mental and psychological health (Kerr and Espie, 2000). Behavioral disturbances are very frequent in ID-epileptic patients and the diagnostic process may be interfered

by seizure frequency, seizure severity, temporality of seizure occurrence, life events, and other socioeconomic indicators (Wilcox and Kerr, 2006).

Gastrointestinal problems are common in persons with ID for a variety of reasons. The most obvious regard the lifestyle and poor physical activity often associated to motor disability and skeletal deformities. In the last few years there is a growing body of literature reporting functional alterations in ASD. Gastrointestinal symptoms are reported between the 22% and 84% in the paediatric population (Horvath and Perman, 2002b, Horvath and Perman, 2002a, Melmed et al., 2000, Nikolov et al., 2009). Gastrointestinal symptoms have been associated to greater severity of irritability, anxiety and social withdrawal (Nikolov et al., 2009). The exploration of the relationship between the physiopathology of ASD and alteration of intestinal microbiota and metabolomes, including neurotransmitter molecules, represent a new research frontier in this field.

CNS ageing and dementia are another challenging issue in PwID. Some genetic syndromes are associated to certain types of dementia, for example it is well-known that persons with Down's Syndrome are at very high risk to develop Alzheimer's disease in their fifties (Holland et al., 2000, Prasher, 1995) reaching the 16.8% prevalence rate (Coppus et al., 2006). The onset of dementia dramatically contributes to a global decline in health status of these individuals including epilepsy, lung disease, mobility problems, visual and hearing impairment, cataract, fractures with increased need for hospitalizations and surgeries (McCarron et al., 2005, Patti et al., 2005). Dementia may also be associated to the onset or worsening of behavioral disturbances (Huxley et al., 2005) and psychiatric symptoms.

Overweight and obesity are major health issues in PwID, especially in higher-income Countries (Fox and Rotatori, 1982, Janicki et al., 2002, Kelly et al., 1986, Rimmer et al., 1993, Rubin et al., 1998). Obesity prevalence is similar in ID as in the general population according to population-level surveys (Emerson, 2005, Yamaki, 2005). Prevalence rates range from 25% and 50% in females and 15% and 45% in males in USA, and slightly lower rates in European Countries and Australia (Rimmer and Yamaki, 2006). Extreme obesity (BMI>40) has been reported to be disproportionately more common in PwID too (Rimmer and Wang, 2005). Gender (female) , ageing, less severe degrees of ID and certain genetic syndromes (i.e., Down syndrome, Prader-Willi syndrome) are risk factors for obesity (Rimmer and Yamaki, 2006). Researches claim environmental factors as the major determinants of this comorbidity. It is possible that antipsychotic treatment, especially Second Generation Antipsychotics (SGAs), contribute to metabolic side effects in this population (Rummel-Kluge et al., 2010).

Organic pathologies are often undetected especially in individuals with severe and profound ID. Indeed, impaired communication and language, reduced awareness of body schemata, altered perception of pain may make the diagnosis very difficult. Moreover, in patients with a restricted communicative repertoire, physical illness may be misinterpreted as apparent problem behaviors (PBs), or psychiatric symptoms. Therefore, in the complex evaluation of PwID it is essential to consider all factors that can influence behavior and affect vulnerability and symptom presentation. The exclusion of physical problems as the cause of behavioral disturbances is the first obligated step of the psychiatric and behavioral diagnostic process in PwID.

Problem behaviors

PBs or challenging behaviors (CB) 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 (Cooper et al., 2007d, Deb et al., 2008, Emerson et al., 1999, Smiley, 2005).

PBs may be defined as all those behaviors that for intensity, frequency, or duration threaten the physical safety of the person or others or restrict access to the community (Emerson et al., 2001b). This interferes with learning, development, and social participation. The most common types of PBs in this population are: physically aggressive behavior, verbally aggressive behavior, screaming, destructive behavior or aggression to property, self-injurious behavior, overly-demanding behavior, oppositional-defiant behavior, and sexually inappropriate behavior (Lowe et al., 2007, Smith and Matson, 2010a). Some authors also include stereotypies. Behavioral difficulties often persist, with relapse and remission periods, and the same individual may show multiple forms of challenging behavior (Lowe et al., 2007).

PBs result from the complex interaction between biological, psychological, social and developmental factors (Griffiths and Gardner, 2002), whereas in some cases genetic causes underlie PBs and impacts directly on the phenotypic expression (O'Brien and Yule, 1995, Tunnicliffe and Oliver, 2011).

In a quantitative perspective, a behavior is considered problematic basing on excessive intensity, frequency or duration. In fact, the same behaviors may be part of the communicative or symptomatic repertoire of the individual, mostly of those subjects with severe cognitive, language and communication impairment. Behaviors may achieve the significance of PB for a large variety of reasons: physical disorders, pain, psychological distress, attempts to achieve a secondary advantage with environmental reinforcements. In general, challenging behaviors may be considered the common final pathway of any kind of distress. CB could also occur as symptoms of psychiatric disorders (de Winter et al., 2011, Emerson et al., 2001a, Felce et al., 2009, Hemmings et al., 2006, Kishore et al., 2005, Moss et al., 2000), 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).

Other risk factors for CBs are co-occurring ASD (McClintock et al., 2003), the level of ID (Emerson and Bromley, 1995, Emerson et al., 2001b), gender (male), young age ((Emerson and Bromley, 1995, Emerson et al., 2001b, McClintock et al., 2003), and overmedication (Matson et al., 2000). The assessment of CBs should be very careful considering all the factors described above, as they are a major cause of misdiagnosis and inadequate treatment. Indeed, the general tendency of most caregivers and of not fully trained professionals is toward a “urgency-guided” management approach, often leading to over-prescription of sedatives and antipsychotics and not based on a solid and scientific diagnostic process.

1.3 AUTISM SPECTRUM DISORDERS

1.3.1 DEFINITION AND DIAGNOSTIC CRITERIA

Autism Spectrum Disorders (ASD) are a group of heterogeneous conditions sharing two key features: impairment of socialization and qualitative deficits of communication, (e.g. reluctance to make eye-contact, lack of appropriate peer relationships, lack of emotional reciprocity, delay in verbal responses, poor conversation skills, lack of pretend play), and restricted and/or repetitive behaviors or interests (e.g. repetitive motor movements, preoccupation with parts of objects, hyperfocused interests) (Briegel et al., 2009, Horovitz and Matson, 2010, Leung et al., 2010, Matson et al., 2009a, Matson et al., 2009b, Smith and Matson, 2010a, Smith and Matson, 2010b, Smith and Matson, 2010c).

The term autism was coined by Eugen Bleuler to describe one of the four fundamental aspects of schizophrenia, the 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 'preference for living in a fantasy world', a gap between the patient's inner fantastic world, inaccessible to reality, and the unlovely environment (Bleuler, 1911). More precisely, the Bleulerian "autism" had nothing to do with the later meaning of social isolation and its theoretical conceptualization of autism did not impact on later discussions about autism.

There is large agreement that the "discover" of autism belongs to the separate works of Hans Asperger and Leo Kanner, who in 1943 and 1944 described some children with clinical picture fitting with the current descriptions of autism. The 'Autistischen Psychopathen' patients described by Asperger were different from those of Kanner in three aspects: 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.

However, this view is quite inaccurate because by the 1920s the term autism had been definitely used in paediatric circles in Europe to label the social withdrawal that small children experienced (Shorter and Wachtel, 2013). In this perspective the transition from Bleulerian autism and the current term has its roots in a literature of clinical descriptions produced between the end of the 19th and the beginning of the 20th centuries. Children with a marked tendency to isolation, poor affective contact, and coldness toward significant others were described under the label of "hereditary insanity". Many of them also had psychosis but a remarkable intelligence, as described in his textbook by Heinrich Schüle, a German physician (Schüle, 1886). By the 1880s similar features associated to catatonia were found in developmentally delayed children. For example, in 1887 the English paediatrician J. Langdon Down associated autistic behavior with catatonia in 'developmental idiocy', although he used neither the term autism nor catatonia. He described those children as poorly reciprocate "he returns your kiss by a bite", inflexibly mute, withdrawn and scarcely reactive regardless of the circumstances around them, and sometimes fascinated by peculiar sensorial stimulations, for example the

rhythm of music. He also described automatic movements of the fingers and rhythmical movements of the body, what now we would call stereotypies (Down, 1887). In 1913 Kraepelin describing a childhood onset form of dementia praecox, accounted for clinical pictures belonging to the current description of autism: he referred to these patients embracing the term autism coined by Bleuler (Kraepelin, 1913). In the following twenty years the term autism ran across the Europe. In that period a Russian paediatric neurologist, Grounia Soukhareva, gave autism its modern meaning of social isolation, she applied to children the Kretschmer's ideas about autism and underlined the association with catatonia (Ssucharewa, 1932). Although she remained almost completely unknown to historians, she gave an important contribution as she had large sample of children to observe. Her work was then continued and expanded in Moskow by Ewa Grebelskaja-Albatz, who in 1934 published a case series on 22 children with autism, psychosis and/or catatonia, but focusing on patients with lower functioning (Grebelskaja-Albatz, 1934, Grebelskaja-Albatz, 1935). Unfortunately, probably due to the language, this remarkable work was forgotten for long time.

Even in USA, some authors had descriptions of young schizophrenic patients who can now be revised as catatonic and autistic, for example in 1930s Howard Potter, Lauretta Bender; Juliette Louise Despert imported this concept of autism in the context of schizophrenia of children (Grebelskaja-Albatz, 1934, Grebelskaja-Albatz, 1935). In this context the credit of Kanner and Asperger was that of an afterthought more than prologue in definitely separating autism from schizophrenia giving to these syndromic pictures an autonomy. Currently, we are still questioning about the relationship between the former and a letter and the idea con a neurodevelopmental continuum has been hypothesized (Insel, 2010, Owen, 2012, Owen and O'Donovan, 2017).

Further advances in the clinical conceptualization of autism is due to Lorna Wing, a British psychiatrist born in 1928, mother of an autistic child and founder of the National Autistic Society in the UK. She 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 still 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 ID. Even in the 1960s children showing several signs of autism, co-occurring mild ID, and childhood psychosis were rediscovered.

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 by international classifications and the definition of Pervasive Developmental Disorder (PDD) was introduced. Five disorders belonged to PDD category: 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 behaviors, anti-social behaviors, 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 ((APA), 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 behaviors 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 behavior, 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 behaviors, interests, and activities (Achkova and 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 behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understand relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, 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 behavior (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 progress. Some authors suggest centring the diagnosis on repetitive behavior and stereotypes, while others on sensorial sensitivity (Billstedt et al., 2007, Happe and Ronald, 2008, Leekam et al., 2007).

1.3.2 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). The recorded prevalence of ASDs has increased dramatically in the last decade 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 (Kim et al., 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 gender 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 ASD 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 and Zoghbi, 2011), 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 and Bourgeron, 2006). Furthermore, autistic symptoms are usually observed in many genetic syndromes, such as fragile X, tuberous sclerosis, phenylketonuria, as well as conditions affecting the first stages of CNS development during pregnancy, for example congenital rubella (Freitag, 2007, Betancur et al., 2009).

Many of the genes associated with autism code for proteins involved in regulating synaptic connectivity and brain functioning (Persico and Bourgeron, 2006, Folstein and Rosen-Sheidley, 2001).

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 and 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 suggested the contribution of chromosome 11 alterations in the pathogenesis of autism, along with the gene coding for the Neurexin 1 (NRXN1), a protein involved in synapse formation and synaptic transmission. Similarly, the 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 too (Autism Genome Project et al., 2007, Sudhof, 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 evidence indicates genetic factors as a major cause of autism, the role of epigenetic mechanisms has been extensively studied. In fact, epigenetic mechanisms that alter gene expression and phenotype without changing the DNA sequences, seem to play a key role in mediating the interaction between genetics and environment in the etiopathogenesis of ASD. For instance, the genetic alterations of gene subsiding epigenetic control of DNA expression across life have been implicated not only in the pathogenesis of ASD but also of major mental health conditions such as schizophrenia (Neniskyte and Gross, 2017).

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, motor deficits and autistic-like behaviors. 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 (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. Therefore, the prenatal exposure to high air pollution containing many toxins impacts negatively on the neurological function and seems to double the risk 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 and colleagues (Boukhris et al., 2016) have recently published several reports suggesting that maternal exposure to selective serotonin reuptake inhibitors during pregnancy would be associated with an increased risk of autism, but this causal relationship does not seem supported by clear evidence (Andrade, 2017b, Andrade, 2017a, Croen et al., 2011, Suri et al., 2014, O'Dowd, 2014).

On the contrary, metabolic problems that affect mothers during pregnancy, especially type 2 diabetes, are significantly associated with an increased risk of ASD, as well as maternal obesity during pregnancy, although further study is needed (Krakowiak et al., 2012, Li et al., 2016).

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, Auyeung et al., 2010) giving a biological basis to the theory of the extreme male brain (Baron-Cohen, 2002).

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

Furthermore, a broad variety of postnatal contributors to autism have been proposed, including: autoimmune diseases (Ashwood and Van de Water, 2004), leaky gut syndrome (Johnson, 2006), vitamin D deficiency (Cannell, 2008), and heavy metal toxicity (Davidson et al., 2004). For the majority of these risk factors, there is no definitive evidence of a causal or co-causal role in the development of ASD. As suggested above, it is plausible that at least an alteration of epigenetic mechanisms is needed to exert the specific final pathway to autism of this variety of factors.

Some researches indicate that oxidative stress may be related to autism in individuals who are genetically predisposed (Kern and 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 and Chauhan, 2006).

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

Among these factors, childhood vaccinations, especially the Measles-Mumps-Rubella (MMR) vaccine, 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 (Afzal et al., 2006, Chen et al., 2004, Taylor et al., 2014, Wilson et al., 2003).

In 2013, Prof. Frank DeStefano and colleagues from the U.S.A. CDC (Centres for Disease Control and Prevention) conducted a study on over 1.000 children with and without autism. This study did not find any link between ASD and the antigens contained in the vaccine, which determine the activation of the immune system. The early exposure to heavy metals was also suspected of increasing the risk of ASD correlated to vaccinations. In particular the hypothesis involved the use of the mercury-based compound thiomersal as childhood vaccines 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 and 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 brain areas related to specific functions, such as social, cognitive, linguistic, and visuospatial processing in children and adults with ASD (Maximo et al., 2014). Currently, 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 and Keller, 2010, Muller et al., 2011). The disconnection of these neural circuits could lead to deficits in complex information processing and integration (Courchesne et al., 2001, Courchesne et al., 2007, Geschwind and Levitt, 2007, Mizuno et al., 2006, Noonan et al., 2009, Turner et al., 2006). The disruption of the typical development of neural circuitries probably involve histogenesis processes alterations since the first phases of CNS development during foetal life and then childhood: various processes may be involved and include neurogenesis, neuronal migration, dendritic development, synaptogenesis, synaptic pruning, dendritic plasticity and myelination. Some researchers 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 differently implicated in the pathogenesis in each individual with ASD, with the result of 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 behaviors, ritualized and restricted range of interests have been related to dysfunction of the orbitofrontal cortex, anterior cingulate cortex, basal ganglia, and thalamus.

Volumetric studies are contradictory as some studies observed increased total brain volume (Minshew et al., 2005), while other found at the opposite a decrease as well as smaller posterior subregions of the corpus callosum (Courchesne et al., 1993, Stanfield et al., 2008, Hardan et al., 2009). Other researchers found microstructural abnormalities mainly concerning a reduction of Purkinje cells of the cerebellum (Bauman and Kemper, 2005). In early knowledge, cerebellum 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 have been described (Eigsti and Shapiro, 2003, Howard et al., 2000, Schumann et al., 2004, Stanfield et al., 2008).

Despite the importance of communication and language deficits in autistic individuals, there are few 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 Fosse et al., 2004, Redcay, 2008, Rojas et al., 2005).

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

Recent evidences provide a better understand of neurotransmitter mechanisms regulating social behavior. Oxytocin and vasopressin neuropeptides play an important role in social cognition, affecting individual differences in social recognition, and parenting or affiliative behaviors. 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 behavior is also mediated by norepinephrine and serotonin systems (Skuse and Gallagher, 2011).

Electrocortical alterations

Some neurophysiological investigations on individuals with ASD reported abnormal frequency range (30-80 Hz) in neuronal synchronization 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 (Endele et al., 2010, Rubenstein and Merzenich, 2003).

Imbalance between excitation, inhibition and increased excitatory-inhibitory (E-I) ratio is a commonly suggested 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., 2016).

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 human ability to relate one each other. When we observe any other performing 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 behavior 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 or features of autism. 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, cannot empathize with the world around them, and do not understand the meaning of the gestures or actions of others (Gallese and 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 behavior. Handling with 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 behavior of oneself or others on the basis of individual ‘internal’ mental states which determine those behaviors (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, behaviors 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 sufferings (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 deficits in ToM have a role in ASD, and more generally in the processes of social cognition. Studies have found that many people with ASD and/or psychotic disorders consciously observe and imitate the behaviors of others. According to these researchers the processing 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, Froese et al., 2013b, Gallagher and Varga, 2015).

1.3.4 PROBLEMS ASSOCIATED WITH AUTISM SPECTRUM DISORDERS

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 suggested that sensory processing problems are more frequent than social interaction difficulties (Baum et al., 2015). This aspect is so significant that DSM-5 included sensory issue among the diagnostic criteria for ASD.

ASD persons may also have a variety of neurological and medical illnesses: epilepsy, gastro-intestinal disturbances, immunity imbalance are the most frequent. Issues related to neurological and medical comorbidities are largely overlapping to those of intellectually disabled persons and have been extensively discussed in 1.2 section.

Problem behaviors

Problem behaviors (PBs or Challenging Behaviors) are common in people with ASD, with a prevalence of 44% (Mattila et al., 2010) which can overcome the 85% in LF-ASD (McCarthy et al., 2010), rather, the co-occurrence of the two conditions increases the risk of PBs comparing to the individual conditions.

Hyper-activity, aggression, self-injurious behavior, irritability, and tendency to moodiness (Emerson et al., 2001b) are often observed in people with ASD. Challenging behavior may also simply be a means of communication and occur most likely in individuals with communication impairment (McClean and 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 et al., 2009b).

The majority of PBs have a complex multifactorial aetiology in ASD including biological, psychological, social and developmental factors. Challenging behaviors can occur as symptoms of other psychiatric disorders or physical diseases, but any particular behavior cannot 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 assessment procedure should consider all risk factors, in order to provide appropriate treatment options and support (Matson and Sturmey, 2011).

1.4 DEPRESSIVE AND BIPOLAR DISORDERS

1.4.1 DEFINITION AND CRITERIA

The modern concept of Bipolar Disorder (BD) is due to Kraepelin (Kraepelin, 1896), who grouped *endogenous psychoses* in two distinct categories: *manic-depressive insanity* and *dementia precox*. Before that time other authors had conceptualized manic-depressive illness as *folie circulaire* (Falret), insanity of double-form (Baillarger) and cyclothymia (Kahlbaum and Hecker) (Snook et al., 2015). Kraepelin distinguishes manic-depressive insanity form dementia praecox for the episodic and recurrent pattern, less or no impairment in cognition and relatively favourable long-term course and outcome.

In 1957 the term *bipolar* was coined by Leonhard to indicate those patients with both manic and depressive episodes comparing to *monopolar* patients only reporting depressive episodes. Subsequently, some authors confirmed this distinction by describing case reports and through familial data (Angst, 1966, Winokour et al., 1969). Other authors proposed unipolar and bipolar patients belonging to the continuum of manic-depressive illness (Goodwin and Jamison, 2007). DSM-III ((APA), 1980) separated Major Depressive Disorder (MDD) and BD putting them together in the chapter of Mood Disorders (MDs). In the same period some authors proposed the distinction of BD type I and II according to the history of manic episodes and only hypomanic episodes, respectively (Dunner et al., 1976). DSM-IV and DSM-IV-TR did not make substantial variations in the descriptions and nosography of MDs, except for the inclusion of BDII along with cyclothymic disorder ((APA), 1994). BDI and II were also included in the tenth edition of ICD under the common label of bipolar affective disorder ((WHO), 1999). In the last four decades a great body of literature regarding MDs have been produced and the concepts of depressive and bipolar disorders are being continuously evolving. In the DSM-5 ((APA), 2013) the panel for MDs made some significant changes. The biggest change is that the MDs category disappeared and was decompose in the two separated categories of Depressive Disorders (DDs) and BDs. In ICD-11 DDs and BDs have been separated too, but remaining under the persisting matasyndromic label of the MDs.

The basic shape of the DSM-5 definition of major depressive episodes (MDE), fundamental for the diagnoses of MDD, BDI and BDII, is substantially unchanged: the presence of five of nine diagnostic symptoms including depressed mood and/or loss of interest and pleasure is required for at least 2 weeks. The severity of symptoms causes a change of the functioning. As in the previous editions, a variety of course and episodic specifiers are provided to facilitate a complete description of the disorder and, for research purposes, to better entail different phenotypes. Specifiers are the same for MDD, BDI, BDII and BD-NOS: they regard remission (partial and full), severity (mild, moderate, severe), peripartum onset, seasonal pattern, and clinical associated features: anxious distress, mixed features, melancholic features, atypical features, mood-congruent and -incongruent psychotic features, catatonia. The course specifier "with rapid cycling" is related to only BDs. MDE is defined by the presence for at least two weeks of five or more symptoms including depressed mood, diminished interest or pleasure, significant reduction or increase of body weight or appetite, sleep disturbances

(both insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy nearly every, inappropriate or excessive feelings of worthlessness, guilt and other holothymic themes, diminished ability to think or concentrate or indecisiveness, suicidality including thoughts of death, recurrent suicidal ideation, suicide attempt or a specific plan for committing suicide. Depressed mood and loss of energy are essential symptoms, alternative one each other.

DDs include along with MDD the newly conceptualized disruptive mood dysregulation disorder (DMDD), relative to children and adolescents, persistent depressive disorder (PDD) which represent the "evolution" of previous dysthymic disorder, and premenstrual dysphoric disorder. Other specified depressive disorders allow the diagnosis for those individuals do not meeting full criteria for other disorders, namely paucisymptomatic depression, short-duration depressive episode and recurrent brief depression.

Except for its repositioning under DDs, at first sight MDD remained unchanged in DSM-5 comparing DSM.IV-TR. Three minor changes have been made in the criteria:

1) The allowance of *mood-incongruent psychotic symptoms* arose some perplexities as it seems inconsequential with the depressive construct and better belonging with the bipolar one (Uher et al., 2014).

2) *Hopelessness* was placed among the subjective descriptors as equivalent figure of depressed mood. This addition was in agreement with some research finding MDD patients potentially reporting hopelessness without sadness and vice versa. The change may broaden the diagnostic boundaries of depression and potentially increase the risk of overdiagnosis (Uher et al., 2014).

3) DSM-5 removed the *bereavement exclusion criteria* relying on clinical judgment the diagnosis of MDE in the context of a significant loss. In spite of the clinical plausibility of this choice, this change provoked significant critiques (Wakefield and First, 2012). On one hand, some studies demonstrated that clinical and associated features, prognosis and response to treatments are similar to bereavement-unrelated MDE, questioning the utility of the differentiation (Kessing et al., 2010). On the other hand, the distinction between bereavement-related MDE, normal reaction to significant loss and complicated grief may appear too subjective and potentially leading alternatively to under- or overdiagnosis depending on the professional.

The relationship of MDD with the other DDs may be somehow challenging. DSM-5 provided that MDD and PDD may co-exist as recurring MDE may superimpose to long-lasting subsyndromal depressive symptoms. Indeed, PDD includes both the DSM-IV-TR concepts of dysthymic disorder and chronic depression. In this vein, the relationship with MDD may be considered ambiguous as it is not completely clear whether or not the meeting of full criteria for the MDE for more than 2 years qualify MDD, PDD or both (Uher et al., 2014). Moreover, it is questionable the legitimacy of equalizing the constructs of former chronic MDE and dysthymia, which has solid and independent historical, epidemiological and clinical features. Even the new conceptualization of premenstrual dysphoric disorder, which is not considered an exclusion criterion for MDD and vice versa, may result ambiguous and the broadening of the criteria might lead to difficulties in establish reliable boundaries with other MDs as well as overdiagnosis.

The definitions of both manic and hypomanic episodes have been radically revised, with significant impact on both BD diagnoses. In a recent paper Jules Angst analyzed pros and cons of the new diagnostic criteria for BD (Angst, 2013), highlighting and discussing the main three changes:

1) The *change of the gate questions* in criterion A is excessively restrictive and may lead to the exclusion of some individuals who were previously diagnosed as BD patients, or their classification as having subthreshold BD. Indeed, DSM-IV and DSM-IV-TR required the presence of elated/euphoric or irritable mood; in DSM-5 the mood change has to be necessarily accompanied by "persistently increased activity or energy levels". This modification is not actually based on reliable data, but it is in contrast with some evidences demonstrating exactly the opposite. A multicentric international study including 5635 major depressive patients clearly showed that any of those three gate questions (euphoric or irritable mood or increased energy levels) is valid on its own to identify BD patients (Angst et al., 2012). In this perspective, the author, as well as others before (Calabrese et al., 2017, Robins and Guze, 1970, Severus and Bauer, 2013), suggested the "*under sizing*" of mood in the diagnosis of MDs in favour of the reappraisal of psychomotricity as key altered function in MDs. In agreement with this point of view, a recent study found that the application of the dyadic criterion reduces the prevalence of manic and hypomanic episodes by about half (Machado-Vieira et al., 2017). By the contrary, other data shew only a minor impact on the prevalence of BDs according to DSM-5 criteria (Fassassi et al., 2014).

2) In the DSM-5 the list of *exclusion criteria* was reduced. One of the most important exclusion criteria removed was the hypomanic switch under antidepressants. If the full hypomanic syndrome persists after the interruption of antidepressants, the BDII diagnosis can be formulated. This modification conforms to some research data suggesting BDII to be actually as prevalent as BDI (Angst et al., 2012). Moreover, substance and medication-induced BDs have been reframed stressing that mood symptoms should disappear when the causative condition is removed: if anything, a diagnosis of BD is more appropriate. In clinical practice this strict causative relationship is often difficult to be ascertained.

3) The introduction of the "*Other specified bipolar and related disorder*" represents the effort of DSM-5 task force to operationalize those subthreshold conditions previously falling under the vague label of Not Otherwise Specified (NOS). It seems also the attempts to maintain a connection between DDs and BDs: this new category includes those conditions in which MDE is associated with subthreshold excitative syndromes, for instance full symptomatic hypomanic presentations of short duration (2 or 3 days), paucisymptomatic presentations or hypomanic episodes superposed to dysthymia. Short duration cyclothymia is also included.

As in the former versions of the DSM, mania and hypomania are both characterized by euphoric, elated or irritable mood and at least 3 out symptoms (4 if the mood is only irritable) from a list of 7 including inflated self-esteem or grandiosity, decreased need for sleep, talkativeness or pressured speech, racing thoughts or flight of ideas, distractibility, increased goal-directed activity or psychomotor agitation and excessive involvement in activities with high potential for painful consequences and risky behavior. The differentiation between BDI and BDII is essentially provided by the chronological and severity of the impairment criteria. The first pertains to the duration of full syndromatic presentation requiring at least one week for BDI and at

least 4 days for BDII. The latter refers to the severity of symptoms which has the shape of a clear and observable variation with respect to the usual functioning for hypomania, whereas for diagnosing mania a more substantial impairment is required in social or occupational functioning or the severity must be is such as to require the hospitalization to prevent harm to self or others. The presence of psychotic symptoms points out to the diagnosis of mania.

In spite of some advances, the underdiagnosis of bipolar patients has to be expected, due to the heterogeneous ranks of MDD with significant implications for treatment strategies. In spite of this effort, some concerns already present for DSM-IV-TR and regarding the overall soft bipolar spectrum remain open. Indeed, the description of Cyclothymic Disorder (CD) has not been changed in DSM-5. CD is defined by the occurrence of "periods with hypomanic symptoms that do not meet criteria for a hypomanic episode and periods with depressive symptoms that do not meet criteria for a depressive episode"; thus, no specific type or cut-off number of symptoms is required. DSM-5 allows the diagnosis of CD, even with a history of hypomania, mania, or depression, but only if the CD came first and lasted for a sufficient period to support this diagnosis. Similarly, ICD-10 included cyclothymia among MDs, providing a rather broad definition of the disorder as "a persistent instability of mood involving numerous periods of depression and mild elation, none of which is sufficiently severe or prolonged to justify a diagnosis of bipolar affective disorder or recurrent depressive disorder". ICD-10 overtly recognized that the disorder is frequently found in the relatives of patients with bipolar affective disorder and that some patients with cyclothymia eventually develop BD. Those definitions are quite appropriate to the reality, but in clinical practice the diagnosis of CD is too often missed, as the majority of cyclothymic patients seek psychiatric treatment for a major affective episode. This could be due to the key issue of the continuity with temperament and personality dispositions, which remains omitted. In fact, both in the ICD-10 and DSM-5 many of the core symptoms, psychological consequences and behavioral abnormalities of cyclothymia are left unmentioned. Excessive emphasis is given to variations in mood, while most of the essential motivational, volitional, emotional and cognitive aspects of the clinical picture are not even mentioned in the diagnostic criteria or among the associated features of CD. Mood reactivity and affective instability, extreme emotionality and impulsivity, which should be considered the true core features of cyclothymia, together with their psychological, behavioral and interpersonal consequences, are described from a different perspective in the DSM-5 criteria for dramatic or anxious clusters of personality disorders as well as in the ICD-10 definition of emotionally unstable and histrionic personality disorders. In the neurodevelopmental perspective similar symptoms _ or a part of them_ have been reframed under the label of *emotional dysregulation*, common not only in childhood and adolescence MDs, but also in ADHD, ASD and other neurodevelopmental disorders as well as in some organic psychiatric correlates (epilepsy, brain traumatic injury, etc.) (Mazefsky et al., 2013, Shaw et al., 2014).

Moreover, DSM-5 introduces a new positioning of mixed episodes: mixed episodes do not exist anymore as independent entities, and mixed features become a specifier. This change represents the attempt to overcome longstanding concerns and actual difficulties in capturing complex mixed affective states with the combinatory model provided by DSM-IV-TR. These difficulties include the need to better capture the highly prevalent

subsyndromal presentations, very common in clinical practice (Vieta and Valenti, 2013). The *mixed features specifier* can be applied to depressive, manic and hypomanic episodes in MDD, BDI, BD II and BD-NOS. Mixed episodes are characterized by full meeting of the criteria for depressive, manic or hypomanic episode, respectively, plus at least three counterpolar symptoms present for most time during the episode. For the (hypo)manic episode potentially overlapping symptoms with MDE, for example psychomotor agitation, have been excluded. The list of depressive symptoms includes prominent dysphoria or depressed mood, diminished interest or pleasure, psychomotor retardation, fatigue or loss of energy, feelings of worthlessness or guilt and suicidality. For the MDE with mixed features all the (hypo)manic criteria are provided except for distractibility. This model creates a new concern regarding the impossibility to solve the unipolar-bipolar dichotomy, usually based on the presence or absence of manic features, often leading to significant rates of misdiagnosis (Bschor et al., 2012, Matza et al., 2005, Nusslock and Frank, 2011, Thase, 2006, Zimmermann et al., 2009). An MDE with mixed features belongs to DDs and the bipolar connection still remains unrecognized: however, in the manual, authors suggested caution in the choice of treatment strategies given the well-documented high rates of conversion to BD. Caution is also suggested given some clinical features specifically associated to mixicity, for example heightened risk of suicidality (Akiskal et al., 2005).

In ICD-11 the clinical utility was the guiding principle of all the changes made comparing to ICD-10 as well as the applicability across transcultural differences. A prototype-based approach was preferred or integrated where necessary. In this vein, the major modification comparing to the previous revisions, not limited to the MDs section but extended to the overall revision, was to create a descriptive guideline accounting for a large variety of descriptions and including boundaries with normality and other disorders, developmental presentations, typical course, comorbidities, and culture- and gender-related attributes (Chakrabarti, 2018, First et al., 2015, Maj, 2011). Comparing to DSM-5, ICD11 offered a more flexible approach to the diagnosis, minimizing excessively complex criteria and somewhat arbitrary thresholds. The counterpart is that the distinction between DDs and BDs is not fully emphasized (Paykel et al., 2012).

The other major effort was the attempt to harmonize as much as possible the eleventh revision with DSM-5, especially in the overall structure. Thus, ICD-11 provided two separated blocks for DDs and BDs: however, the superordinate category of MDs was maintained in order to stress the traditional link between the two. A simplification was made as the description of all mood episodes was provided at the beginning of the MDs section. Individual diagnoses of different MDs were subsequently established according the differential patterns of mood episodes over time.

Few conceptual changes have been made in the DDs section:

1) Diagnostic symptoms were grouped in "*clusters*". For example, reduced energy and fatigue were included in the "neurovegetative cluster" and not mentioned as essential features. In this vein, the "affective cluster" resulted predominant for the diagnosis.

2) ICD-11, according to DSM, added *functional impairment* as essential feature. The *severity* subtypes (mild, moderate, severe) based on type, number and severity of the symptoms were retained across the versions in spite of the lack of evidences of their utility and reliability (Ayuso-Mateos and Lopez-García, 2012).

3) ICD-11 provides clinical and course specifiers, here called "*qualifiers*", used for single as well as for recurrent depressive episodes. Some qualifiers were maintained from ICD-10, for example melancholia and remission qualifiers, whereas others were borrowed by DSM-5 such as the seasonal pattern, the peri-natal onset and "with prominent anxiety symptoms". The latter, similar to the DSM-5 "anxious distress" specifier, is supported by a body of research indicating the presence of severe anxiety during depression as an important phenotypization index as well as prognostic and treatment factor (Uher et al., 2014). This qualifier has not to be confused with "*mixed depressive and anxiety disorder*" accounting for those clinical pictures commonly found in primary-care settings, and characterized by subthreshold depressive and subthreshold anxiety symptoms (Chakrabarti et al., 2012, Moller et al., 2016, Paykel et al., 2012). This category, put under DDs in ICD-11, has not been included in DSM-5.

4) Dysthymic disorder diagnosis has been enriched with more in depth descriptions than both ICD-10 and DSM-5, emphasizing the subthreshold chronic course (Phillips, 2012). The superposition of MDE is allowed as in DSM-5, given full criteria for dysthymic disorder preceding the onset of MDE. In ICD-11 the boundaries with depressive personality disorder are better defined as well as the latter represents an exclusion criterion for the diagnosis of dysthymic disorder.

The description of BDs and, for instance, manic and hypomanic episodes in ICD-11 was in agreement with DSM-5's. ICD-11 also added to persistent euphoria, irritability, expansiveness, and lability, the *changes in activity or energy* as essential criterion for the diagnosis. The inclusion of an additional feature regarding effects of psychopharmacological medications, allowing the diagnosis of BD in case of persistent (hypo)mania beyond the known effects of these treatments, follows the DSM-5 indication. The ICD-11 qualifiers of BDs are similar to DSM-5 specifiers and pertain remission, severity, psychotic symptoms, melancholia, comorbid anxiety, perinatal onset, seasonal pattern, and rapid cycling.

In contrast with DSM-5, ICD-11 retained the previously accepted definition of mixed episode (Maj, 2012), probably receiving the critiques to DSM mixed specifier (Malhi and Porter, 2016). Moreover, the MDE with mixed features is poorly differentiated from mania and hypomania. By the contrary, and according with a part of the classical literature (Kraepelin, 1913, Salvatore et al., 2002), ICD-10 emphasized as core features of mixed states the rapid alternation of depressive and counterpolar symptoms, rather than the simultaneity of full criteria (Maj, 2012). This definition, more adherent to classical and modern conceptualizations of mixed states as well as to clinical experience, is less operationalizable. In ICD-11 additional and detailed descriptions of excitative symptoms and qualifiers are provided in the attempt to reduce this gap.

ICD-11 is aligned to DSM-5 in including for the first time in the ICD system the BDII diagnosis, considering the vast amount of research supporting its independency into the bipolar spectrum regarding familial, presentation, course and outcome (Strakowski, 2012). Contrary to DSM-5, with the exception of cyclothymia, no further soft bipolar spectrum condition has been included given the paucity of replicated data (Strakowski et al., 2011, Zimmerman, 2012). The description of cyclothymia is in agreement with DSM-5 but further efforts have been made to distinguish cyclothymic mood instability from mood fluctuations ranging in the normality.

On the other hand, similar attention has been dedicated to differentiate psychotic mood disorders from clinical pictures pertaining the schizophrenic spectrum (Strakowski, 2012).

1.4.2 EPIDEMIOLOGY

Depressive Disorders

A large body of literature indicates DDs, namely MDD, as a major source of functional impairment and disability in Western Countries (Spijker et al., 2004, Kessler and Bromet, 2013, Moussavi et al., 2007, Bromet et al., 2011, Greenberg et al., 2015). MDD has been associated to poor socio-economic status (Kessler, 2012), lower educational level (Kessler et al., 2003), mental and physical health burden (Grant and Harford, 1995, Greenberg et al., 2015, Hasin et al., 2005, Kessler et al., 2003, Kessler et al., 1994, Regier et al., 1990, Vancampfort et al., 2015), and mortality (Kessler, 2012). Prevalence data on DDs and their epidemiologic correlates are mostly relative to pre-DSM-5 period. Large nation-wide surveys found lifetime prevalence rates of MDD ranging from 3.0% (Weissman et al., 1991) and 16.2% (Kessler et al., 2003). Despite the extent of the prevalence gap, all the studies agreed that MDD would have an early onset with a low risk in early teens, a linear increase in the second decade with the achievement of the peak of onset around 30 years. The rates of onset resulted slightly lower during the third and the fourth decade whereas a significant reduction was found after 60 years (Kessler et al., 2003). All the community surveys also found that persons with a lifetime diagnosis of MDD were more vulnerable to the lifetime development of further psychiatric disorders (Regier et al., 1990, Kessler et al., 1996). For example, in the National Comorbidity Survey Replication (NCS-R) almost the 75% of MDD patients had another lifetime psychiatric diagnosis, mostly anxiety disorders (59.2%), substance use disorders (24%), and impulse control disorders (30%). The rates of simultaneous co-occurrence of MDD with other diagnoses in the previous 12 months resulted similar. Higher severity was associated to higher rates of psychiatric comorbidities (Kessler et al., 2003).

Recently the results of National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III), a large national US study including more than 35000 participants, have been published (Hasin et al., 2018). In the survey the DSM-5 have been employed. The12-month and lifetime prevalence rates of MDD were 10.4% and 20.6%, respectively. Women showed in both the measures about doubled rates (13.4% and 26.1% among women vs. 7.2% and 14.7% among men): the study confirmed the gender difference previously reported (Goodwin and Jamison, 2007, Hasin et al., 2005, Mojtabai et al., 2016). MDD resulted associated to lower age and economic status, the mean age at onset of MDD was estimated between the second and the third decade and the median duration of the longest MDE was around 6 months (Hasin et al., 2018). Suicidality was also explored considering its detection when depression had been estimated to be at its severity peak: suicidality (including thoughts of death, desire of dying and contemplating suicide) resulted to be a depressive feature in almost the half of MDD patients lifetime comparing to around the 30% only considering the MDEs in the previous 12 months (Hasin et al., 2018).

In agreement with previous studies both 12-month and lifetime MDD were significantly associated to all the psychiatric comorbidities in the NESARC-III. Particularly prominent association emerged with drug use disorder (lifetime OR 2.5), higher than for alcohol or nicotine use disorders, and borderline personality disorders, stood out from other personality disorders (lifetime OR 4.4). The risk of the co-occurrence of an anxiety disorder was near to 4 times higher comparing to non-MDD participants, with the highest OR of 4.9 for GAD (Hasin et al., 2018).

The most interesting results of the NESARC-III regarded the two clinical specifiers. The anxious/distressed specifier characterized 74.6% and 70% of lifetime and 12-month MDD participants respectively, whereas the mixed-features specifier criteria was met in the 15.5% and 20.6% of lifetime and 12-month MDD participants, respectively. Both the specifiers resulted significantly associated with clinical and course indices of higher severity of the disorder. Specifically, MDD participants with positive lifetime mixed specifier more frequently belong to the MDD severe group. Mixed specifier was associated to earlier age at onset with mean age lower than 3 years comparing to non-mixed participants, but also to major treatment utilization with the highest gap reported in the need for emergency treatments and hospitalizations. Mixed MDD patients also reported significant higher impairment in all the functioning areas explored (mental health, social and emotional-role functioning). Suicidality was significantly associated to mixed features with very significant rates in general and particularly a doubled prevalence rate of suicide attempts (12.0% in non-mixed vs. 22.6% in mixed patients). The results are similar for the anxious/depressed specifier even if slightly lower in magnitude comparing to the mixed specifier. Noteworthy, there was a high co-occurrence between the two specifiers (the 92.8% of participants meeting the mixed specifiers also met the anxious/depressed) (Hasin et al., 2018).

Adverse experiences and traumatic events during childhood may be risk factors for depression in adulthood. Socioeconomic disadvantage, maltreatment, and social isolation during childhood have been associated to depression in adults as well as a greater number of adverse experiences would increase this risk (Danese et al., 2009).

Regarding familial and genetic load for MDD, conclusions from studies have to be drawn more cautiously than for BD, as “MDD bag” is a highly heterogeneous container, probably including very different conditions. The most part of the literature examined this issue via the assessment of the offspring of depressed parents. Results suggested that a family history for the MDD would represent the strongest and most reliable risk factor for the development of the disorder with 3- to 5-fold increase among first-degree relatives (Williamson et al., 2004). The most interesting and reliable data pertain longitudinal studies of MDD in children and adolescents. The early onset of MDD may join more homogeneous phenotypes. MDD children and adolescents have been reliably sub-grouped according to three different illness trajectories (Schubert et al., 2017): onset during childhood with severe symptoms and persistence into adulthood (childhood persistent), onset during childhood with moderate to severe symptoms but decline during adolescence and young adulthood (childhood limited) and subtle and mild onset during adolescence with gradual increase of the severity of depressive symptoms over time (late adolescent onset) (Kwong et al., 2019). The first and the latter trajectories were associated to poorer outcome, whereas the late adolescent onset was also related to polygenic risk of depression indicating

a significant genetic load in this subpopulation (Kwong et al., 2019). By the contrary, childhood limited depressions seem more correlated to circumstantial environmental stressors or events (Yaroslavsky et al., 2013).

Some longstanding studies observed a common transnosographic familial liability among depression and other psychiatric disorders, from time to time anxiety disorders specifically GAD and panic disorders (Weissman et al., 1986, Kendler et al., 1994), bulimia and alcohol dependence (Weissman et al., 1986): these data are not fully replicated.

Some more recent studies focusing on structural and functional brain anomalies in youth at familial risk for MDD found specific alterations in regions involving emotion and reward as possible vulnerability markers for MDD preceding the onset of illness (Gotlib et al., 2014). This liability is partially shared with other disorders, namely BD (Nasrallah et al., 1989, Whalley et al., 2013a, Whalley et al., 2013b). These promising findings support the idea of a familial-mediated functional underpinning in MDD.

Bipolar Disorders

In the last decades a great amount of epidemiologic research has been conducted worldwide underlining the magnitude, correlates and consequences of BD. In the World Health Organization World Mental Health (WMH) surveys BD resulted the second cause of disability (Alonso et al., 2011).

The lifetime prevalence of BD type I (BDI) according to community-based studies ranges from 0.0% in Nigeria (Gureje et al., 2006) to 3.3% in USA (Grant et al., 2005). The twelve-month prevalence is slightly lower, achieving a rate of 2.0%. As expected, with more inclusive disorder definitions, rates become even higher when BD type II (BDII) and the overall Bipolar Spectrum Disorders (BPS) are included: for example, in the WMH survey the cross-national prevalence of the overall BPS was 2.4%, with prevalence rates of 0.6% for BDI, 0.4% for BDII and 1.4% for subthreshold BD (Merikangas et al., 2011). The majority of the studies reported BDI rates higher than BDII (Merikangas et al., 2011, Wittchen et al., 1998). This datum may be explained by the difficulties to diagnose hypomania in most patients, who tend to seek treatment only during depressive phases. The requirement by current diagnostic systems of MDE criteria to be met, or, the fact that probably, most patients with hypomania may have also experienced at least one manic phase may contribute to the underestimation of BDII prevalence (Merikangas and Paksarian, 2015). Among youngsters the prevalence of BD is estimated around 1.8% (Van Meter et al., 2011).

The incidence of BD in the general population has been also evaluated (Chou et al., 2011, de Graaf et al., 2013, Grant et al., 2009). In a recent large epidemiological study, the one-year incidence resulted 0.53% and 0.21% for BDI and BDII, respectively (Grant et al., 2009). A Dutch study reported a three-year BD incidence rate of 0.41% among adults aged 18 to 64 (de Graaf et al., 2013). Similar incidence rates were found among the elderly (0.54% BDI; 0.34% BDII) (Chou et al., 2011). In spite of these numbers and the high burden of the disorder, only about the 50% of the adults and the 20% of the adolescents receive appropriate treatments.

The mean age at onset of BD is around 18 years both in males and females (Zimmermann et al., 2009) with the first onset usually reported during adolescence or early adulthood for most patients (Lewinsohn et al.,

2002). Indeed, in prospective cohorts the prevalence rate reaches 2% at age of 21 years (Lewinsohn et al., 2002, Cannon et al., 2002).

Historically, research reported similar rates of BD in males and females (Grant et al., 2009, Merikangas et al., 2007), confirmed by more recent data in adulthood (Kessler et al., 2012) and in youth (Kozloff et al., 2010). By the contrary, the WMH surveys found BDI and subthreshold BD to be more common lifetime in males, whereas females had more frequently a lifetime diagnosis of BDII (Merikangas et al., 2011). It is possible that worldwide socio-cultural gender-mediated differences may influence the presentation of the illness.

Regarding other demographic correlates, epidemiologic studies found as risk factors for BD low socioeconomic status and poor educational level (Grant et al., 2009, Grant et al., 2005, Merikangas et al., 2007). Moreover, BD rates are higher among separated or divorced comparing to never married individuals (Subramaniam et al., 2013). No significant ethnicity differences in BD rates have been definitely detected, also because of the difficulties in including sufficiently homogeneous and large subsamples of distinct ethnic groups.

Experiences of stressors and traumatic events during childhood are considered risk factors for BD (Mortensen et al., 2003): the likelihood to develop BD is increased especially in the victims of physical and sexual abuse during childhood (Wells et al., 2010) but an association have been reported also with physical and emotional neglect, parental violence and criminal behavior (Nierenberg et al., 2010), and economic adversities (Gilman et al., 2015). These risk factors are non-specific for BD and shared with other psychiatric disorders as well as substance abuse, ADHD, anxiety disorders, depression and suicidality, suggesting other general mechanisms mediating the causal effects of traumatic events. A potential recall bias may also influence the reliability of these data (Merikangas and Paksarian, 2015).

One of the strongest and most consistent risk factors for BD is a family history for BD, especially in first-degree relatives. First-degree relatives of BD patients showed a 6.5 to 8-fold increase in the relative risk to develop BD (Aukes et al., 2012, Lichtenstein et al., 2009, Wilde et al., 2014). The high heritability of the disorder is confirmed by twin studies reporting an 8-fold increase in the risk of BD in monozygotic twins of bipolar patients than in dizygotic twins (Smoller and Gardner-Schuster, 2007). The genetic load seems stronger for BDI than for BDII and MDD (Merikangas et al., 2013, Vandeleur et al., 2014).

Despites these observations, the results of molecular genetic studies are still inconclusive. The majority of genome wide association studies (GWAS) have substantially failed in identifying genes reliably associated to the disorder and effect sizes resulted often too small (Merikangas and Paksarian, 2015). The largest GWAS performed including thousands of patients and controls found two genome-wide significant loci: the first on chromosome 12, near to CACNA1C gene, and the second one on chromosome 11, near to ODZ4 gene ((Psychiatric, 2011). CNVs have been reported to be also implicated but results are not conclusive (Malhotra and Sebat, 2012, Bergen et al., 2012). Small sample sizes and methodological differences in recruiting probands may have affected the results. Mostly, the poor differentiation among different phenotypes of BD and the lack of endophenotypes would have caused excessive heterogeneity.

Mixed episodes

The overall mean prevalence rate for mixed episodes is about 30% (McElroy et al., 1992), varying from 6.7% and 66% according to narrower or broader definitions, respectively (Cassidy et al., 2008). Predominantly manic mixed states showed a prevalence of around 65%, with higher rates in females than in males (Cassidy et al., 2008), whereas predominantly depressive states have been studied at a lesser extent (prevalence rates ranging from 20% to 70% (Azorin et al., 2012, Benazzi, 2008, Goldberg et al., 2009) but no gender differences have been reported (Akiskal et al., 2005, Azorin et al., 2012, Benazzi, 2008, Perugi et al., 2001). Patients with mixed states, depressive and manic indistinctly, seem to report a younger age at onset and the mixed episode occurs in the early stages of the illness comparing to pure episodes eventually occurring along the illness course (Azorin et al., 2012, Benazzi, 2008, Cassidy and Carroll, 2001, Goldberg et al., 2009, Gonzalez-Pinto et al., 2007, Perugi and Akiskal, 2005, Valenti et al., 2011).

Comparing to pure manic patients, mixed manic patients exhibit a worse course of the illness with higher number and longer duration of the episodes (Martin-Carrasco et al., 2012), severer functional impairment (Rosa et al., 2009), higher rates of relapse, higher rates of psychiatric comorbidities as substance use, suicidality and shorter free intervals (Cassidy et al., 2008, Gonzalez-Pinto et al., 2007, Valenti et al., 2011, Baldessarini et al., 2010, Azorin et al., 2009). Mixed depressive patients have similar associated features with the addition of higher rates of rapid cycling and mood-incongruent psychotic features (Akiskal et al., 2005, Azorin et al., 2012, Goldberg et al., 2009, Perugi et al., 2001).

1.4.3 ETIOLOGY

The etiology and pathophysiology of MDs are still unknown and probably involve several biological mechanisms. The research in this field may have suffered for the heterogeneity of the MDs patients. It is probable that the etiopathogenetic cause is not unitary.

(Fries and Kapczinski, 2015) Stress and its biological correlates have been implicated in the pathophysiology of depression and BD long time ago with evidences of the dysfunction of cortisol and hypothalamus-pituitary-adrenal axis (HPA) (Grunze, 2011, Knorr et al., 2010). In some patients with MDD and BD the negative feedback loop subsiding the suppression of cortisol secretion by adrenal cortex appears impaired, as demonstrated by the response to dexamethasone infusion (Daban et al., 2005), CRH and DEX/CRH tests (Roy et al., 1986, Rybakowski and Twardowska, 1999, Schmider et al., 1995). Excessive glucocorticoids may have central effects as the induction of regression of dendritic processes in neurons and inhibition of neurogenesis (Sapolsky, 2000), the increase of glutamate concentrations in hippocampal synapses, contribution to mitochondrial dysfunction and oxidative stress (Du et al., 2012) with long-term effects on genes' expression (Quiroz et al., 2008). Literature shows opposite and inconclusive data about whether HPA overactivity is a trait or state marker of MDs (Swann et al., 1992, Deshauer et al., 2003, Wedekind et al., 2007).

The research about the neural substrates of depression mostly focused on of the functional and anatomical correlates of emotional information processing dysfunctions and over-reactivity or loss of resilience to stress. Dysfunctional activity in the salience network, including amygdala, dorsal anterior cingulate cortex, and

anterior insula as well as impaired thalamic network, have been demonstrated in MDD patients: these abnormalities would be correlated to impairment in processing negative stimuli (Hamilton et al., 2012, Pessoa and Adolphs, 2010). The regulation of emotion and reward processing seem also impaired in MDD patients: the former deficit would be underpinned by altered activation of medial, dorsal and ventral regions of the frontal lobe (Erk et al., 2010). The impairment of reward processing is related to reduced activity in striatal circuit (Gotlib et al., 2014). The anomalies of some brain structures have been associated to MDD and may involve subcortical grey matter, with the evidence of reduced volume of hippocampus (Gotlib et al., 2014); cortical gray matter thinning across frontal, temporal, parietal cortices (Peterson et al., 2009), prefrontal cortex (Amico et al., 2011), anterior insula and anterior cingulate (Foland-Ross and Gotlib, 2012); functional connectivity alterations in some white matter structures such as temporal (e.g., (Zhu et al., 2011) and occipital (Kieseppa et al., 2010) lobes and along midline structures (e.g, (Zhu et al., 2011, Kieseppa et al., 2010).

Neuroimaging studies regarding BD pathophysiology and progression suggested that neuroanatomical and functional alterations occur in specific brain regions rather than in the whole brain (Fries and Kapczinski, 2015). Among the numerous findings, the most replicated is the enlargement of lateral ventricle (Kempton et al., 2008), whose magnitude is also correlated with the number of illness' episodes (Brambilla et al., 2001b, Strakowski et al., 2002). Smaller total brain volume (Frey et al., 2008), reduced volume of left putamen and left inferior prefrontal gray matter (Lopez-Larson et al., 2002), reduced hippocampal volume (Javadapour et al., 2010) and relative increase of amygdala volume (Bora et al., 2010) have also been associated to the progress of the disorder. By the contrary, changes in shape and volume of basal ganglia, especially striatum, was described as hallmark of BD since the onset of the illness (Fries and Kapczinski, 2015). According to these evidences, neuropathological studies have shown reduction of the glial cells pool and density, alterations of density and size of specific neuronal populations mostly regarding prefrontal and limbic cortical regions (Rajkowska, 2002).

Cell death and loss of resilience have been suggested by biochemical studies implicating a variety of mechanisms. Signs of increased apoptosis have been found in oligodendrocytes of frontal cortices of dead bipolar patients (Uranova et al., 2001). Excitotoxicity plays a key role, mostly mediated by glutamate and calcium. Increased serum and prefrontal concentrations of glutamate have been found during mania and depression (Altamura et al., 1993, Hashimoto et al., 2007, Hoekstra et al., 2006), which are related to elevated intracellular calcium levels and disturbed calcium homeostasis in MDs (Warsh et al., 2004). Excessive cytosolic calcium may activate a cascade of intracellular mechanisms leading to cytoskeletal degradation, protein misfolding, oxygen reactive species (ROS) overproduction and, finally, apoptosis (Warsh et al., 2004). Oxidative stress, mitochondrial dysfunction, altered inflammatory response, and their relationship with alterations in calcium, dopamine and glutamate-mediate neurotransmission have been hypothesized to be implicated with BD (Andreazza and Young, 2014). For example, in post-mortem studies mitochondrial genes resulted downregulated in hippocampus (Lieberman et al., 2007, Konradi et al., 2004) and dorsolateral prefrontal cortex (Iwamoto et al., 2005, Sun et al., 2006), regions just implicated in the pathophysiology of BD by functional neuroimaging studies. The finding that antioxidant enzymes are altered (e.g(Andreazza et al.,

2007, Benes et al., 2006, Machado-Vieira et al., 2007) is related to unbalance toward increase of oxidative stress. These alterations may regard several enzymes such as SOD, CAT, GPx and GST: genes codifying for these enzymes have been found downregulated in the hippocampus of bipolar patients (Benes et al., 2006). On the other hand, it seems that during acute illness phases, both depression and mania, the activity of SOD is much increased (Andreazza et al., 2007, Machado-Vieira et al., 2007, Gergerlioglu et al., 2007). Whether or not SOD hyperactivity is limited to acute episodes or is also present during euthymic intervals has to be clarified (Savas et al., 2006). Researchers also found indirect signs of increased oxidative stress, for example increased lipid peroxidation (e.g. (Andreazza et al., 2008) and increased levels of nitric oxide (e.g. (Gergerlioglu et al., 2007).

There are increasing evidences of the involvement of inflammatory processes both in the periphery and brain. In BD patients are reported altered levels of peripheral cytokines depending on the phase (Brietzke et al., 2009, Kapczinski et al., 2009) and the stage of the illness (Kapczinski et al., 2008, Kauer-Sant'Anna et al., 2009): the studies reported increase of pro-inflammatory cytokines (IL-2, IL-6, TNF-alfa), anti-inflammatory cytokines (IL-1beta, NF-kB) and antagonist proteins of IL-1 receptor. Even post-mortem studies found altered mRNA levels of IL-1beta, NF-kB and IL-1R subunits in the frontal cortex of BD patients (Rao et al., 2010). Other acute inflammatory response proteins have been shown elevated in the plasma of BD patients such as haptoglobin, C-reactive protein and complement factors (Dickerson et al., 2007, Maes et al., 1997). Some findings support the hypothesis that in late stages of the illness the anti-inflammatory mechanisms are less responsive and effective as well as illness progression may be the resultant of the accumulation for years of oxidative damages (Andreazza et al., 2008, Kauer-Sant'Anna et al., 2009).

Oxidative stress may also be triggered and maintained by direct inhibition of the mitochondrial electron transport, as it is the case of the Ca2+-channel. An involvement was suggested by GWAS studies (regarding CACNA1C), consistent findings of increased intracellular levels of CA2+ in bipolar patients (Kato, 2008) and functional imaging studies (O'Donovan et al., 2009, Vacher et al., 2008).

A relationship between neuroinflammation and neurotransmission has been hypothesized: for example, a proinflammatory state may activate increase consumption of tryptophan, the precursor of serotonin, with increasing levels of tryptophan catabolites and dysregulation of the neurotransmitter system and mitochondrial metabolism (Berk et al., 2011). Other neurotransmitters potentially involved in or by oxidative stress are dopamine and glutamate. Specifically, an increase in dopamine cerebral production leads to increase activity of monoamine oxidase (MAO) enzymes with overproduction of ROS, poorly compensated along the course of the illness (Berk et al., 2007, Chen et al., 2008, Andreazza et al., 2009). Similarly, an increased release of glutamate, via the hyperstimulation of NMDA receptors, augments the intracellular passage of Ca2+ with final overproduction of ROS, mostly nitric oxide (Coyle and Puttfarcken, 1993).

Inflammatory proteins are not involved in the pathophysiology of BD and MDD only throughout the relationship with oxidative stress but also via a their direct signaling potential. Recent clinical studies demonstrated that BD patients show higher rates of autoimmune and infective diseases as well as a tendency toward atopy (Benros et al., 2013, Perugi et al., 2015). Research on MDD reported similar findings (Miller et

al., 2009). Many preclinical and clinical studies also showed that inflammation may induce depression and major depressive and bipolar patients display markers of inflammatory activation (Miller et al., 2009, Dantzer et al., 2008, Schiepers et al., 2005). Murine studies support the hypothesis for example indicating that the role of inflammation may be mediated by glycogen synthase kinase-3 (GSK-3), whose inhibition by lithium and other medications has been hypothesized to lead to mood stabilization (Klein and Melton, 1996, Stambolic et al., 1996).

Human studies regarding the role of GSK-3 as well as other transduction proteins (phosphatidylinositol 4,5-bisphosphate PIP2, protein kinase C PKC) are inconclusive but suggestive, especially because implicated with the effectiveness of lithium. Inositol depletion and abnormal PKC signaling could be involved in the pathophysiology of MDs (Jope et al., 2015).

Also signaling pathways enhancing the expression or neurotrophins such as BDNF may be deficient in MDs, with subsequent impairment of multiple processes going from neurotransmission to neurogenesis. Such impairments have been found in both depression and BD. Epigenetic mechanisms are probably the best candidate, as demonstrated by the evidence increased methylation of BDNF gene promoter I in patients with BDII (D'Addario et al., 2012). Blood levels of BDNF are reduced in depressive patients (Autry and Monteggia, 2012, Duman and Li, 2012) as well as in bipolar patients (Pittenger and Duman, 2008). Rodents models confirmed these findings: for example, the hippocampal infusion of BDNF in depressive rats may attenuate depressive-like symptoms (Duric et al., 2013). On the other hand, some researchers found that mood stabilizers and antidepressants may induce up-regulation of neurotrophins (Chiu et al., 2013, Duric et al., 2013, Eisch and Petrik, 2012). The disruption of BDNF signaling can lead to decreased dendritic spines and arborization, neuritic dystrophy and degeneration, and neuronal atrophy (Teixeira et al., 2010). These alterations in neurogenesis probably find their clinical correlates in the cognitive deficits of some individuals with MDD and BD and are concordant with the evidence from neuroimaging studies of faster age-related cortical neuronal loss (Brambilla et al., 2001a).

1.4.4 CLINICAL FEATURES

As noted by Goodwin and Jamison in their famous textbook (Goodwin and Jamison, 2007), the distinction between *unipolar* and *bipolar* forms of MDs significantly changed over time, since the original descriptions used both terms to indicate “phasic or cyclic course of recurrent episodes, characterized by autonomous *endogenous* features and clear functional impairment”. By the contrary, classificatory systems since DSM-III enlarged the boundaries of depression including under the label *unipolar* a heterogeneous population of patients still including endogenous recurrent disorders as well as all depressions, for example, reactive ones, “neurotic” forms, bereavement-related, depressive precursors of dementias etc. This problem has never been solved in the following versions of the DSM. In this perspective, results from studies about differences of depression in MDD and BD patients have obvious limitations. However, some suggestions can be drawn. Comparing to MDD patients, BDI patients showed earlier age at onset with a narrower range for the onset, major number of episodes, namely depressive, shorter length of both the depressive episode and the cycle. BDI

is equally prevalent among males and females, whereas MDD depression is more common among females. BD is also associated to a wider extent of psychiatric comorbidities, substance use, affective temperaments, mostly hyperthymic and cyclothymic, higher or better documented familial and genetic load. Even response to antidepressant treatments shows some differences as BDI patients report faster responses and higher rates of tolerance to antidepressants and (hypo)manic switches (Goodwin and Jamison, 2007).

The heterogeneity of the "bag" also affected BDs, but at least the distinction in BDI and BDII brought some clarity. As written in the above paragraph, BD-I patients are characterized by history of one or more full-blown manic episodes, even if hypomanic episodes may occur during the course of the illness. The diagnosis of BDII requires a story of MDE and hypomanic episodes. However, the research on BDII has suffered for poor reliability of the diagnosis with current operational criteria, mostly because of difficulties in recollecting the history of past hypomania (Andreasen et al., 1981, Dunner and Tay, 1993). In fact, BDII patients mostly seek treatment when depressed, and during depression patients are even poorer at recalling previous hypomanic episodes. Moreover, hypomanic patients usually do not have insight of their condition: even after its conclusion they tend to misattribute to environmental factors and circumstances their peculiar emotional state and behaviors. This is the main reason why in clinical practice the use of multiple informants as well as the use of descriptive behaviors more than a mere list of symptoms may be much more appropriate in improving the diagnosis of BDII.

Depression

Depression is usually characterized by a decrease or slowing in most aspects of emotion and behavior: speed and amount of thought and speech, energies, ability to experience pleasure, sexuality and leisure may all be reduced at a variable degree. The severity of symptoms may vary from mild mental and physical slowing to most severe cases of psychomotor arrest associated with stupor, delusions, hallucinations and catatonic symptoms, sometimes resulting in life-threatening conditions. Depression, with peculiar exceptions, is the most frequent presentation in BD patients spending about the 40% of time depressed comparing to 9% of the time in (hypo)mania (Judd et al., 2002). At a cross-sectional examination there are no pathognomonic signs of bipolar depression to be distinguished from unipolar one (Snook et al., 2015). Meanwhile, some studies found atypical features of depression, such as psychomotor retardation, hypersomnia and hyperphagia, psychotic features and mood lability to be more common in bipolar depression (Mitchell et al., 2008). Main functions perturbed during depression as well as in mania are mood, activity and behavior, cognition and perception.

1. *Mood*

Depressive mood is usually bleak, pessimistic, and despairing. This affective color is often associated to feelings that things are meaningless and the person lost the capacity to experience pleasure. There may be a general flattening involving not only mood *strictu sensu*, but also motivation, physical experience and cognition. Irritability, anguish and anxiety, anger, emotional lability, sensitivity and paranoia may be present. Variations during the day with alternation and medley of all these figures are common with differential patterns among patients and across the course of the episodes or different episodes in the same patient.

The impairment of emotionality and the widespread dulling may elicit a generalized fear of insanity, especially when unreality feelings or experiences are associated. Beyond the basic affective tonality, even the mood reactivity to external stimuli is compromised, with the exception of some specific depressive forms, for instance called *atypical*. Indeed, comparing to melancholic depression, atypical depression is characterized by preserved mood reactivity. No significant differences in the severity of depression have been reported across the diagnosis of unipolar disorders, BDI and BDII (Goodwin and Jamison, 2007, Mitchell et al., 2001).

2. *Activity and Behavior*

Activity and behavior may be slowed in typical forms of depression. A general reduction of energies and a primary disturbance in volition are expressed by asthenia and fatigue, reduced or completely lacking activities, social withdrawal with more or less extensive impairment in daily functioning in few areas (familial, relationships, occupational). Full psychomotor retardation is quite rare but more common in BDI than BDII or unipolar patients (Parker et al., 2000, Benazzi, 2002). At the opposite, in some forms of depression psychomotricity may be characterized by a general activation ranging from a painful and unpleasant feeling of inner tension, up to restlessness and psychomotor agitation. According to classical descriptions but not to current classification, psychomotor agitation is a sign of the so-called *agitated depression*, included by Kraepelin among mixed states. Psychomotor agitation seems to be more common in BDII patients (Benazzi, 2002).

Facial expression, posture, movement and the general appearance of the patients can be very suggestive of depression. The reactivity and the coherence of mimics with environment is often lost and the expression of face and eyes may communicate sadness, anguish or fear. Movements are often slowed and reaction are sluggish. Gestures and body communication are reduced to the minimum. The general appearance may suggest reduction in self-care as well as an age older than the actual. Speech alterations are consistent with the general psychomotor slowing with a global reduction of its volume and increased latency of response (Mitchell et al., 2008, Sadock et al., 2009).

Neurovegetative alterations are often early signs: depressive patients report specific patterns of insomnia as well as qualitative alterations and non-restorative sleep. Vivid and disturbing nightmares are common. By the contrary, hypersomnia can be the hallmark of atypical depression. Unipolar patients more commonly experience insomnia, both initial as early morning awakenings (Mitchell et al., 2008). Appetite may be altered too, with general decrease often associated to gastrointestinal somatization, up to severe and debilitating anorexia. As for sleep, the polarity of the alteration is opposite in atypical depression: appetite can be excessive and may cause hyperphagia usually associated to preference or actual craving for specific foods, mostly carbohydrates. Corresponding weight variations are a reasonable consequence.

Psychotic depression, considered the severest form, has similar symptoms of non-psychotic depression but usually at a worse degree with additional delusions and hallucinations. These forms may more easily be associated to catatonia, whose belonging to psychotic dimension has been extensively questioned (Fink, 2013).

3. *Cognition and perception*

Mental activity including formal and content aspects as well as specific cognitive functions likely attention, procedural speed, memory etc., may be variously impaired: they are usually slowed. However, only in psychotic forms of depression symptoms in this area reach the severity level of consciousness alteration, delusions and hallucinations. By the contrary, inappropriate and continuous ruminations regarding holothymic figures such as hypochondriac, worthlessness, and guilt ideas, as well as a broad range of suicidal thoughts including vague ideas about death till precise plans for suicide, are common in the majority of depressive patients. Cognitive distortion about these negative thoughts may induce misinterpretation of past and current events (Sadock and Sadock, 2007). Similar to ruminations, incapacity to decide and a more general difficulty to think are present. Comparing to other neurological conditions, for example in the early stages of some dementias, depressive patients usually complain about their cognitive deficits often associating a hopelessness sense of impossibility of restitutio ad integrum. This feeling is distinctive of all depressive phases in any patient, even in those who have already experienced previous episodes as well as recovery: in spite of past experiences, they are often not sensitive to reassurance as the current moment would seem never-ending. Delusional mood-congruent contents are usually accentuations of prevalent ideas of non-psychotic depression and may regard guilt and worthlessness, mashed-up with somatic, religious or financial issues, ruin, sinfulness, illness, prosecution and never-ending sufferings themes. Auditory hallucinations (or pseudo-hallucinations) are usually denigrator and threatening in content. Delusions have been reported in 12% to 60% of bipolar depressive episodes (Black and Nasrallah, 1989, Carlson and Strober, 1979), less common than during mania (Goodwin and Jamison, 2007, Sadock et al., 2009). Hallucinations, more frequent in mania than in depression, are less commonly reported in both polarities. Clinical research suggested that psychotic symptoms are independently associated to unipolar and bipolar depression (Charney and Nelson, 1981, Coryell and Tsuang, 1982, Frances et al., 1981, Glassman and Roose, 1981, Nelson et al., 1984, Spiker et al., 1985).

Mania and hypomania

In mania and hypomania acceleration and sharpness are the core features (Snook et al., 2015). Mood is heightened and overreactive, rapidly oscillating among euphoria, elation, irritability and dysphoria, and a subjective feeling of well-being is present. Psychomotricity is increased and fastened as expressed by quicker thought with a sense of clarity, larger volume of and faster speech, increased energy levels with motor activation, increase of activities, reduced need for sleep, hypersexuality and impulsivity. Reduction of inhibitions and impaired judgement are distinctive features. Positive changes in self-esteem including at the extreme pole grandiosity, paranoia and megalomaniac delusions may be present.

The severity and the duration of these mood, cognitive and behavioral disturbances define the differences between mania and hypomania. During hypomania such alterations are of moderate entity comparing to the disastrous consequences of mania, often disrupting life arrangements of people suffering for it and their families. According to different temperamental and personality structures, for example anankastic and depressive, hypomania may be even lesser evident, without the usually observable variations. Rather, for some

persons hypomanic phases remain unrecognized or remembered as "the only periods in the life they were really fine, and self-confident, and successful".

1. *Mood*

Mood is elevated with some qualitative differences between mania and hypomania. In hypomania self-confidence, elation and cheerfulness prevail, but with easy irritability. Classical descriptions underlined the labile and volatile nature of hypomania (Goodwin and Jamison, 2007). Feelings of well-being, the so-called *eutonia*, are another fundamental feature. In acute mania these characteristics are exaggerated and patients may appear euphoric, joyful and expansive but mood may abruptly change in anger, rage and dysphoria. In some cases, dysphoric nuances may predominate. Jocularity is usually associated to euphoria, often reaching the level of clamorous, disturbing and socially inappropriate behavior.

2. *Activity and behavior*

Overactivity should be considered the true core criterion of mania and hypomania. The level of increased energy and the reflexes on psychomotricity are diversified across the severity continuum. Overactivity refers to reduced fatigability, increased finalistic activities, physical hyperactivity, social disinhibition as well as rashness and impulsivity, aggressiveness and agitation. Behavior may become erratic, disorganized and violent in severe mania: these patients may appear bizarre, paranoid, impulsive, and grossly inappropriate.

Insight and self-awareness are affected in both hypomania and mania going from a loosening of judgment leading to over-planning and wrong or hasty romantic or occupational choices, up to frankly inappropriate and dangerous behaviors and complete lack of the insight of the illness and of the consequences of their behaviors. As in depression, neurovegetative patterns are involved, especially sleep. The reduced need for sleep is a very early sign of (hypo)manic switch, and manic patients may sleep only for two or three hours per day without feeling tired the next morning. This aspect differentiates it from insomnia. Sexual appetite and sexually-oriented behaviors are increased too and sometimes associated to promiscuity.

3. *Cognition and perception*

Thoughts are fast, accelerated in hypomania and mania across a severity continuum from racing thoughts up to flight of ideas and loss of associations. Other formal disturbances of thought and specific cognitive deficits can be found on this continuum as well as tangentiality, assonance associations, disorganized thought and distractibility of various degree. In hypomania associational fluency is furthered and can be associated to the subjective feeling of mental clarity and improved cognitive ability: however, mostly because of the co-occurrence of distractibility and inconclusiveness, such a feeling is not always accompanied with a real improvement of performance. Usually, the loss of association and disorganization are associated to the severest forms of mania and psychosis. Distractibility becomes pervasive and thinking may result incoherent, in these cases alertness and orientation can be affected. These features are prominent in dramatic but rare cases of *delirious mania*, characterized by abrupt onset and a sort of crepuscular state associated with subtotal insomnia, highly pervasive and bizarre hallucinations, stupor, confusion, and sudden shifts from melancholia to mania. Psychotic symptoms are reported in about two third of BDI patients (Goodwin and Jamison, 2007). The themes of delusions as well as of illusions and hallucinations are usually on a megalomaniac background and may

involve religious, political, financial or romantic thoughts. Perceptual disturbances are usually aligned with thought contents.

By definition, psychotic symptoms are not present in hypomania. However, a soft form of grandiosity with increase in self-esteem, increased self-confidence and fluency in sociality, is a common feature. Some kind of sensitivity, soft and volatile paranoid impressions can also be present.

Mixed episodes

Mixed states as the simultaneous occurrence of opposite polarity affective symptoms have been described at the end of 19th century (Kraepelin, 1896, Weygandt, 1899) and categorized in six subtypes according different combination of alterations in the three fundamental dimensions involving affectivity: mood, motor activity, and ideation. The subtypes were depressive mania, excited depression, unproductive mania, manic stupor, depression with flight of ideas and inhibited mania. These descriptions currently preserve their validity from a clinical point of view. Mixed states are common in BD, whereas there are not reliable data regarding MDD, given the too recent modification of the definition. As different definitions have been adopted, prevalence rates vary significantly across studies.

The presence of mixicity has relevant implications for prognosis and treatment. Mixed episodes are associated to worsening of the illness' course and worse cross-sectional outcome. For example, the combination of depressive hopelessness and manic energy and impulsivity underlie a substantial increase in suicide risk (Swann et al., 2013). Temperamental factors may predispose to mixed features: in fact, depressive and hyperthymic temperaments are associated with higher rates of mixed episodes as the natural disposition of the person seems to influence and color the presentation of the affective episode. Thus, mania superposed to depressive temperament may result in a mixed manic episode, whereas depression in hyperthymic individuals has high probability to be diagnosed as a mixed depressive episode (Perugi et al., 1997). That innate pathological emotional features may constitute a bridge with mixicity, is a new and intriguing hypothesis linking emotional dysregulation of neurodevelopmental disorders and BD. Few data are available to confirm this hypothesis, but for example two recent studies, one in children and the other in adults with MDE (Purper-Ouakil et al., 2017, Vannucchi et al., 2019a), confirmed that ADHD is associated to mixed features of depression. Frequencies of mixed versus classic manic features were not systematically studied in adults with other neurodevelopmental disorders, namely ID and ASD.

Mania or hypomania with mixed features may more commonly present with prominent dysphoria, irritability, increased speed of thought and speech but also simultaneous or rapidly alternating depressed mood, depressive feelings such as guilt, anhedonia and poor energy (Snook et al., 2015). Anguish and anxiety may be pervasive. Depression with mixed features is in continuity with "pure" depressive forms with agitation or irritability and distinguishing them is a matter of numbers and a tailored job: the most suggestive signs of mixed features during depression are increased of goal-directed activities and reduced need for sleep (Ketter, 2010).

1.5. PSYCHIATRIC COMORBIDITY IN INTELLECTUAL DISABILITY AND LOW-FUNCTIONING AUTISM SPECTRUM DISORDERS

1.5.1 GENERAL AND DIAGNOSTIC ISSUES

The prevalence of mental disorders in PwID is up to four times higher than in the general population (Cooper et al., 2007d). However, the concept of dual diagnosis is relatively recent, originated in the '(P., 2007). Prior to that period, despite the sparse presence of descriptions and case series about psychiatric presentations in PwID, the dominant opinion in the scientific community was that psychiatric disorders could not occur in PwID, especially in those with worse severity of the ID (Earl, 1961). Various explanations were given, including a lack of consensus on which problems in ID should be considered as mental health problems (Holland and Koot, 1998). This long-lasting preconception has had a negative impact and restraining effects to the research on the specific phenomenological and psychopathological features in ID, and to the development of effective assessment procedures as well as reliable data about management and treatments.

A variety of reasons are implicated in the debate on this field and, from a practical perspective, are the cause of a very complicated psychiatric diagnostic process in ID. These reasons can be grossly distinguished in those pertaining the ID condition *per se* and the peculiar psychiatric phenomenology in ID; on the other hand, there are those specifically addressing the psychiatric diagnosis and the methodology of the assessment.

Intellectual distortion, psychosocial masking, diagnostic overshadowing, appropriateness, developmental baseline exaggeration, and neurovegetative vulnerability, all may lead to atypical presentations of PDs in ID and complicate the diagnosis.

Intellectual or *cognitive distortion* refers to the complex set of difficulties in introspection capacity, in defining one's own life experiences, and in communicating states of uneasiness or suffering (Cooper et al., 2003, Sovner and DesNoyers Hurley, 1986). Although cognitive distortion may regard at some degree even milder forms of ID, it is as more interfering as the severer is the ID, mainly when ID is associated with severe language limitations or its absence, communication problems and sensory dysfunctions. These limitations affect the recognition of thought disorders as well as internalizing symptoms such as anxiety, depressed mood and related complex feelings, for example worthlessness and guilt (Einfeld, 1992, Marston et al., 1997), suicidal ideation or diminished ability to think (Smiley and Cooper, 2003).

Furthermore, given their poor verbal capacities, PwID may be passive, inclined to acquiescence and may show deviations from the norm in attributing meanings to communicative contents because of frequent peculiarities in the experiential range (Sovner and DesNoyers Hurley, 1986). These attitudes belong to *psychosocial masking*. For example, people with borderline intellectual functioning or mild ID have been reported to be quite capable of describing about their own behaviors and feelings (Bramston and Fogarty, 2000, Deb et al., 2001a, Moss et al., 1996). However, even in these cases suggestibility, acquiescence, attention deficit, trouble with temporal sequencing, or distractibility, may determine considerable difficulty in providing a full account of their own feelings and experiences.

The most discussed interfering aspect of the psychiatric diagnosis in ID pertains to both a conceptual and a practical level. As discussed in chapter 1.2, previous versions of DSM placed MR/ID on Axis II along with

the personality disorders, while Axis I included 'major' psychiatric disorders (depression, psychosis, etc.). The placement of PDs and MR/ID on separate axes represented the expression of the denial of a possible co-occurrence among them. As research developed and knowledge challenged this axiom, this division seemed to be anyway functional to reduce *diagnostic overshadowing* (Reiss et al., 1982). Diagnostic overshadowing is the difficulty to attribute the observed or referred dysfunctions to the basic condition of ID or to a comorbid psychiatric disorder (Deb et al., 2001b, Jopp and Keys, 2001, Reiss et al., 1982, Reiss and Szyszko, 1983). The supposed effect was to avoid the tendency of clinicians engaged in evaluations of PwID to focus almost exclusively on intellectual and adaptive functioning, ignoring other important information on overall mental health. However, in most cases this separation has had the opposite effect, reducing the relevance of pathoplastic role of MR/ID on psychopathology and clinical presentations. Diagnostic overshadowing can lead to a lack of systematic psychiatric assessment and therefore suboptimal treatment and care (Szymanski et al., 1998, Yoo et al., 2012). Adaptation deficits, poor skills and communicative impairment further hamper the diagnosis. The complex framework of PBs and the concerns regarding their relationship with PDs are connected to this issue (Reiss et al., 1982, Reiss and Szyszko, 1983, Ross and Oliver, 2003). In chapter 1.2 the multifactorial causality of PBs has been outlined. In fact, PBs are not necessarily signs of psychopathology and the clinician should consider that people with more severe ID have a restricted repertoire of communicative behavior: PBs may be caused by physical illness and pain, as well as any kind of environmental, emotional or psychological distress. This is particularly difficult when behaviors qualitatively pertaining to PBs, for example self-injury, aggressiveness and stereotypies, are part of the usual behavioral repertoire of the person or there are background behavioral disturbances (Hurley, 2008).

Clinicians should be specifically trained to overcome this diagnostic challenge in PwID (Werner and Stawski, 2012). Some concepts may guide the diagnosis: all the behaviors and alterations have to be contextualised in the set of previous life experiences, cultural, and environmental influences, but mostly according to the *actual developmental level* of the person. For example, in adults with severe ID the adaptive and emotional development may be estimated around 12-18 months of age comparing to neurotypically developed persons. These factors impact on the presentation of eventually co-occurring symptoms, which often is atypical, chaotic, intermittent, fluctuating, masked, mixed, or poorly defined (Bouras et al., 1999, Sovner, 1986). In addition, the symptomatology of PDs in ID is often characterised by *neurovegetative vulnerability*; pains, organ dysfunction, and circadian rhythm disorders are frequently the main expression of emotional dysregulations (Costello and Bouras, 2006). In this perspective, the precise knowledge of the baseline functioning of the PwID is fundamental to notice significant and suggestive variations. According to the concept of *baseline exaggeration*, PBs or other behaviors and functioning parameters might indicate the onset of a co-occurrent PD when a sustained variation in frequency, severity and duration of usual behaviors is reported as well as the abrupt onset of PBs previously not reported, once other causal factors have been excluded (Moss et al., 2000, Sovner and DesNoyers Hurley, 1986, Sturmey and Ley, 1990). The course of the behavior in respect to other possible symptoms of a PD would represent the main reference to decide whether the considered behavior can be considered a symptom equivalent (Charlot, 2005).

The state of the art provides inconclusive suggestions. Some studies demonstrated a relationship between PBs and PD (Emerson et al., 1999, Felce et al., 2009, Hemmings et al., 2006, Kishore et al., 2005, Moss et al., 2000, Rojahn et al., 2004), particularly strong in individuals with lower level of functioning (Felce et al., 2009), and some behavioral equivalents have been identified for specific symptoms (Hurley, 2006). By the contrary, other studies found no evidence that PBs were behavioral equivalents of PD (Tsiouris et al., 2003) and some authors sentenced PBs and maladaptive behaviors to be interpreted as nonspecific indicators of emotional distress rather than atypical symptoms (Rojahn and Meier, 2009).

Atypical clinical presentations of PDs, including maladaptive behaviors, lent support to the need for research in this field and for the development of adapted criteria for PDs in ID, although some authors concerned that most studies suggesting atypicality of psychiatric manifestations in PD had failed to offer external validators for this hypothesis (Ross and Oliver, 2003). Unfortunately, a vicious circle affects achievements: the lack of reliable criteria, adapted to all the degrees of ID, implies the insufficiency of assessing instruments. Subsequently, the methodology of the studies are very heterogenous and results are by definition inconclusive and often poorly generalizable. In fact, the pragmatic application of current standardized criteria (both DSM and ICD) could, at some extent, show reliability in less severe degrees of ID (Clarke and McKenzie, 1994, Marston et al., 1997, McBrien, 2003, Meins, 1995, Pawlarcyzk and Beckwith, 1987, Werner and Stawski, 2012). The same criteria are instead poorly useful in most persons with more severe ID (Cooper and Bailey, 2001, Sovner and DesNoyers Hurley, 1986). This represent a significant bias in the interpretation of clinical and epidemiological studies: most studies about PDs in ID have been conducted in persons with mild to moderate ID (Ross and Oliver, 2003), but even when including severe and profound ID, studies found higher rates of PDs in mild subjects (Paclawskyj et al., 1997). It remains unclear whether the result is due to true differences according different ID levels or it is only the reflex of the scarce sensitivity to PDs in severe and profound ID.

The diagnostic criteria of the current nosographic systems, including the DSM-5, ICD-10 and ICD-11, 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 informants (e.g. caregiver, and family), and require detailed information on the psychopathology that are not fully applicable to PwID. On the other hand, the framework of PBs is lacking in any of the nosographic systems (Cooper et al., 2003), and rather, in neurotypical persons behaviors commonly found in ID persons, namely aggressiveness, self-injury and stereotypies, have different explanations and implications and cannot be equalize. Some reviews across the last three decades concluded that the use of unmodified standard diagnostic criteria may be inappropriate in ID (Cooper and Collacott, 1996, Davis et al., 1997a, Janowsky and Davis, 2005).

Some authors coined the concept of *behavioral equivalence* to describe alternative and atypical manifestations of PDs in ID (Lowry and Sovner, 1992, Sovner and Hurley, 1982). The evaluation is always based on direct observation of behaviors and the person's way of interacting with the outside world through the knowledge of precise meanings in the context of various environmental factors. This method requires the interview of one

or more care-givers with a detailed knowledge of the person. The purpose is not to rely on self-report. Later, other authors argued that this observational method was promising but needing systematic studies including large number of patients since it had been applied only in case reports and case series (Ross and Oliver, 2003). In order to improve diagnostic sensitivity of clinicians, the Royal College of Psychiatrists (UK) and the National Association for Dual Diagnosis (USA) have respectively produced adaptations of the ICD-10 and DSM-IV-TR called Diagnostic Criteria for Learning Disability (DC-LD) (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 the updated to DSM-5 version of DM-ID2 (Fletcher et al., 2016). Both the DC-LD and DM-ID-2 provide a variety of examples with detailed descriptions of most categories of PDs. It represents a first important step on behalf the improvement of psychiatric diagnostic process in ID and toward the reduction of the utilization of residual categories. At this regard, there are few unfortunate issues: at first, these manuals are poorly known and used among psychiatrists and their impact on clinical practice is being of lesser extent than expected. Secondly, adaptations are actually very accurate and based on clinical literature. However, the literature is not solid and replicated in some psychiatric fields (e.g. bipolar disorders, addictive and related disorders etc.) with the result that for some categories not exhaustive adaptations were provided.

Another issue regards the reliability of the source of information. As already told, specific cognitive, adaptive and communication features of most PwID make them not completely reliable subjects to be directly assessed. Some features of PD, such as sense of hopelessness or worthlessness, suicidal ideation, delusional perception, distortion of self-rule body, are very complex and require a high level of expressive language, abstract thinking, conceptualization, memory, and self-awareness. An attempt to involve patients in their own evaluation should be done, mostly in mild ID, but caution in the interpretation of the information is required (Bertelli, 2015). For example, when ASD co-occurs with ID, the lack of social skills may produce withdrawal behaviors after the exposure to social environment resembling paranoid reactions, as well as typical autistic self-talk when associated to mood or anxiety symptoms might be confused with hallucinatory behaviors.

Thus, the usefulness of available "significant other" to provide or integrate information on the onset and course of psychiatric symptoms is undisputable. Nevertheless, also what others report can be characterised by many troublesome issues. When the informant is a family member it is not infrequent that atypical presentations of PDs are difficulty understood or remembered (Costello and Bouras, 2006, Mikkelsen and McKenna, 1999). Moreover, it is widespread belief that all problems of PwID are inevitable and unchangeable (Costello and Bouras, 2006, Reiss and Szyszko, 1983), and proxies are often poorly prone to believe or accept that the PwID may have an additional mental health issue and deny the presence of psychiatric symptoms. Minimizing attitudes are often sustained by fear for psychotropic medications. Both familial care-givers and staff members may have at this regard opposite attitude, emphasizing the connection between PBs and a supposed PD in order to obtain medications. This peculiar aspect is correlated with the burn-out of the care-giver. In other occasions, both family members or other care-givers tend to "revise" information according to their interpretation of symptoms and behaviors leading both to under- or over-estimation of the type and the severity of the

psychiatric problem (Bertelli, 2015). The literature indicates some proxy factors influencing this kind of evaluation, such as the cultural level and other personal characteristics as well as the nature of the relationship and the affective and practical involvement (Pickard and Knight, 2005, Petry et al., 2009). Thus, integrating information from different sources, such as familiars, carers, or other proxies is recommended.

A certain number of assessing instruments have been developed to detect psychopathology in ID, some general screenings, others area- or disorder-specific tools, based on modified standardized criteria (Feighner et al., 1972, Sovner, 1986, Sovner and Hurley, 1983) or novel diagnostic systems (Matson et al., 1991, Moss and Goldberg, 1991, Reiss, 1987). However, the majority of the 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). An integrated or combined approach with mixed categorical and dimensional properties could be helpful.

1.5.2 EPIDEMIOLOGY

PwID can experience the full range of mental disorders, and there is evidence that PDs occur more commonly than observed in the general population. PDs are frequently underdiagnosed or misdiagnosed, and can markedly reduce cognitive and adaptive functioning.

Prevalence rates of PDs in PwID extensively vary across studies, ranging from 10 to 75% (Bouras and Drummond, 1992, Bradley et al., 2011, Cooper et al., 2009, Deb et al., 2001a, Jacobson, 1982, Lund, 1985). As already outlined in the paragraph above, this heterogeneity is mainly due to methodological problems relative to sampling and ascertainment of the psychopathological condition. ASD and, even at a lesser extent, anxiety and mood disorders resulted the more frequently diagnosed disorders (Cooper et al., 2007b).

In this vein, the heterogeneity of the results requires an interpretation effort within the context of each study (Smiley, 2005). For example, the setting of the study may make the difference according to selection bias of samples in which PDs and behavioral problems may be actually over- or underrepresented. The former is the case of those studies performed in psychiatric services. On the other hand, the studies conducted within administratively defined populations such as rehabilitative services, residences, independent living locations, etc., might be considered more representative of the overall ID population (Cooper, 2019).

Nonetheless, there is a certain agreement that the mean prevalence is around four-fold higher than in the general population. Moreover, the 25-44% of PwID has at least one PD, the 21% have two and the 8% three or more (Cooper et al., 2007b).

1.5.2.1 Prevalence of psychiatric disorders in intellectual disability

The point prevalence of PDs in ID found in a milestone study performed by Cooper and her colleagues was about 40%. The rate was reduced to 28.3% excluding PBs and 22.4% also excluding ASD (Cooper et al., 2007d). The authors highlighted 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). These rates were similar to those found in another important population-based study made in Scotland (Census, 2011) and reliant on self- or proxy reports, found that 23.9% of ID adults reported comorbid PDs comparing to the 5.2% of the adults without ID in the same population (Observatory, 2016). The incidence of PDs in adults with ID, excluding persons with only PBs, has been reported to be 12.6% over a two-year period; 8.3% for affective disorders, 1.7% for anxiety disorders and 1.4% for psychotic disorders (Cooper et al., 2007d, Cooper et al., 2007c, Morgan et al., 2008).

The prevalence of unipolar depression in PwID is estimated about 3.8%, bipolar disorder 1.3%, and manic episode 0.6% (Cooper et al., 2007c, Morgan et al., 2008). The epidemiologic data regarding mood disorders will be discussed in the following chapter. The prevalence rate of anxiety disorders was found to be approximately 3.2% using DC-LD criteria. Point prevalence of individual anxiety diagnoses resulted 1.7% for GAD, 0.4% and 0.2% for agoraphobia and panic disorder, respectively (Reid et al., 2011). Psychotic disorders in intellectually disabled adults were estimated ranging from 2.6% to 4.4% according to different diagnostic criteria (Cooper et al., 2007b, Cooper et al., 2007d).

Prevalence rates of PTSD vary substantially, from 2.5 to 60 % (Mevissen and de Jongh, 2011). Obsessive-Compulsive Disorder (OCD) has been less extensively studied in ID persons. OCD features have been described as occurring within the behavioral phenotypes of specific genetic syndromes such in Down's syndrome (Pary, 2004), Prader-Willi syndrome (Dykens, 2004) and in permutated Fragile-X patients (Schneider et al., 2016). In a clinical sample of moderate-to-severe intellectually disabled adults, the 9.4% shew over-the-threshold OCD symptoms (Holden and Gitlesen, 2004).

Problematic eating behaviors including formal eating disorders (EA) have been found in about one third of PwID, reaching the 80% rate in individuals with more severe impairment and PBs (Gal et al., 2011, Matson and Kuhn, 2001). Regarding the prevalence of anorexia nervosa, bulimia and binge eating disorder (BED) prevalence rates are more uncertain and related studies often do not clearly explain how diagnostic criteria were applied to this population (Hove, 2004). In a well-conducted study including mild to profound ID patients (Hove, 2004), the rates of total eating disorders were 22.7%, 29.9% and 29.4% in mild, moderate and severe/profound ID patients, respectively. Most of the comorbidity were accounted by BED, almost four-fold higher than the rate showed by psychiatric obese outpatient with average IQ (Ricca et al., 2000).

Rates of co-occurring personality disorders in ID shew the higher across-studies variability, ranging from 1% to 91% in community-based samples and from 22% to 92% in hospital settings (Alexander and Cooray, 2003). A reasonable intermediate result should be the 19.1% for personality disorder-NOS and 8.7% for borderline personality disorder in a study conducted by Wieland and colleagues (Wieland et al., 2013).

1.5.2.2 Prevalence of psychiatric disorders in low-functioning autism spectrum disorders

Psychiatric comorbidity in adults with ASD is highly frequent and may represent the main reason for medical and psychiatric help request. The wide overlap between some symptomatologic features of autism and some PDs may complicate the correct framework in this population (Bakken et al., 2010, Clarke et al., 1999, Ghaziuddin and Zafar, 2008).

The prevalence rates of PDs in adults with ASD range from 16% to 35% (Psychiatrists, 2014).
The prevalence of depression is estimated between 15% and 42% (Ghaziuddin et al., 2002, Matson and Cervantes, 2014)and most studies indicated unipolar depression to be the most frequent comorbid disorder in ASD, both high- and low-functioning (De Bruin EI, 2007, Ghaziuddin et al., 2002). Some authors suggested that the prevalence of BD is instead underestimated (Raja and Azzoni, 2008), reporting rates ranging from 3% and 9%, depending on the features of the samples (Rosenberg et al., 2011, Stahlberg et al., 2004).
Psychotic symptoms are not infrequent and this comorbidity represents a crucial diagnostic issue. However, few studies investigated it. Two population studies showed a prevalence rate of psychotic disorders ranging from 4.4% (Cooper et al., 2007b) to 18% (Tsiouris et al., 2011). Similar findings were reported also in clinical studies, with percentages between 7% and 16% (Hutton et al., 2008, Mouridsen and Sorensen, 1995). More specifically, in low-functioning ASD prevalence rates are around 15% (Leyfer et al., 2006, Psychiatrists, 2014).
Anxiety in adults with ASD is reported to be 7%-22% (Ghaziuddin et al., 2002, Matson and Cervantes, 2014). Social anxiety and GAD were the most frequent (22%), while panic disorder and agoraphobia represented the 13% and 15%, respectively (Lugnegard et al., 2011).
In people with ASD, the rate of exposure to trauma in childhood is estimated between 25% and 45% (Costello and Angold, 2000, McCloskey and Walker, 2000), while the risk of developing a PTSD after trauma ranged from 5% to 45% (McCloskey and Walker, 2000). The lifetime prevalence rate of PTSD in this population is estimated between 6% and 8% (Stallard, 2006).
OCD prevalence rates ranged from 7% to 24% (Leyfer et al., 2006, Psychiatrists, 2014). This comorbidity is particularly hard to be correctly framed as over-, under- and misdiagnosis is frequent, mainly due to large overlap of symptoms. In PwID the lack of defence psychism may further hamper the diagnosis.
Similarly, a considerable overlap may be also found among ASD and some personality disorders, mostly cluster A and C: indeed, many trait features of ASD patients overlap with criteria for schizoid, schizotypal, avoidant, obsessive-compulsive, and narcissistic personality disorders' DSM criteria. In a recent report on 54 young adults with ASD diagnosis, about half of the participants also met criteria for a PD according to DSM-IV-TR criteria: approximately two-thirds of the men and one-third of the women met criteria for only 4 PDs: schizoid, schizotypal (cluster A), avoidant, and obsessive-compulsive (cluster C) (Lugnegard et al., 2012). Reliable data in this field are inconclusive.

1.5.2.3 Co-occurrence of ASD in ID: additional vulnerability factor for psychiatric comorbidity

Whether or not persons with low-functioning ASD are at increased risk of developing further psychopathology than PwID without autistic features still remains an unanswered question. Indeed, few studies considered this issue with systematic comparisons. Some literature suggests an increase of the psychiatric vulnerability when ID and ASD co-occur, estimated 5-fold higher than in only-ID persons (Bradley et al., 2004).
To address this issue, our research group recently performed a systematic mapping of the literature including papers published since 2004 to 2016 (Vannucchi et al., 2017a). We identified 15 papers meeting the inclusion

criteria of the research and comparing PDs rates in adults with ID or low-functioning ASD. We found somehow contradictory results. Given the already discussed methodological problems and heterogeneity across the studies, we found rates ranging from 16% to 30.4% for MDs, 12% and 47.8% for anxiety disorders, 17 and 21.7% for schizophrenia spectrum disorders and around 47% for OCD [(Bakken et al., 2010, Bradley et al., 2004, Lunsky et al., 2009, McCarthy et al., 2010, Thalen, 2011, Tsakanikos et al., 2006). According to different assessing instruments and psychopathological parameters, ten papers of the selected fifteen (Bakken et al., 2010, Hill and Furniss, 2006, Hove and Havik, 2010, La Malfa et al., 2007, LoVullo and Matson, 2009, McCarthy et al., 2010, Smith and Matson, 2010b, Thalen, 2011, Totsika et al., 2010, Tsakanikos et al., 2006) reported higher rates or severity or both of psychiatric symptoms in ID/ASD probands comparing to only-ID, suggesting that ASD may actually represents an additional vulnerability factor for the development of further psychopathology in ID individuals. Moreover, it is possible to extrapolate that also increasing severity of autistic symptoms could be related to further psychopathology as well as more PBs and adjustment issues. In this vein, was not surprising that in two of these papers also considering the use of psychotropics the authors reported higher load of medications in ID/ASD patients (LoVullo and Matson, 2009, Tsakanikos et al., 2006). Two studies did not confirm this result, but it is possible that they referred to different samples and typology of patients as they were among those studies not observing differences in psychopathologic presentations (Lunsky et al., 2009, Melville et al., 2008).

1.5.3 CLINICAL FEATURES

1.5.3.2 Clinical features of psychiatric disorders in intellectual disability

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 up to psychogenic polydipsia, hyperventilation, increased urinary frequency, anger, sweating, avoidance behavior, agitation, and excessive motor activity (Cooray and Bakala, 2005). Sometimes anxiety disorders, mostly panic attacks, may be cause of fugue and escape with, paradoxically, the enactment of apparently impulsive and risky behaviors. Even aggression and self-injurious behaviors are often seen in clinical practice. This observation is in line with some studies reporting that PwID exhibit challenging behaviors such as aggression or self-injury as learned dysfunctional coping strategies, especially in those with greater difficulty in communication (Cooray and Bakala, 2005, Stavrakaki, 2002). Panic attacks characterized by derealization and depersonalization are not uncommon in clinical practice with PwID, but such symptoms are often misdiagnosed as psychotic manifestations due to the difficulties of patients in describing the associated unreality feelings. In these cases, typical neurovegetative symptoms may be reduced or may remain in the background or, alternatively, they might be interpreted as an alarm state.

Psychotic disorders

The prevalence of psychotic symptoms in ID seems three-time more frequent than in the general population (Ayub et al., 2015). The diagnosis of psychosis is based on complex assessing procedures and the referred subjective experience and beliefs regarding thought contents and perceptions are usually crucial. This represents a challenge point in PwID and requires a careful and prolonged effort for the clinician to correctly interpret new onset symptoms and behaviors. Moreover, intellectually disabled people with limited verbal skills may exhibit strange behaviors and communicate unusual thoughts basically. On the contrary, many of the same behaviors that might indicate psychosis can be interpreted as ID features when the story of the patient is not correctly collect. If a PwID says that his name has been mentioned in the radio, or in television, it is not sufficient to diagnose a reference delusion; the developmental age of the person should be considered in the interpretation. PwID may also think that someone is trying to control their own actions, but it can be basically true when they require support by others, and it is possible that their apparent distress is mostly related to the poor self-awareness of the ID condition more than to actual broadcasting and influencing delusions. On the other hand, delusion contents may be simple in this population: for example, grandiose delusions can consist in the certainty that they can drive a car. Such a simplicity could divert the interpretation toward minimizing the symptoms.

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

Personality disorders

Features of borderline personality disorder, such as self-injurious behavior, impulsive behaviors and affective lability, often occur in PwID (Mavromatis, 2000). Attention-seeking and dramatic reactions as well as adhesiveness and dependence behaviors or lack of empathy and regret are also common and condition the interpersonal attitudes. However, communication deficits and maladaptive behaviors can make a personality disorder very difficult to be diagnosed in this population, especially in those with more severe impairment (Alexander and Cooray, 2003, Wilson, 2001). Some authors concern the validity of the construct in ID persons, because by definition the full organization of the personality requires a developmental level corresponding to that of young neurotypical adults.

Eating Disorders

Numerous and heterogeneous types of eating and feeding problems affect PwID (Gal et al., 2011). Common dysfunctions are pica (Hove, 2004), rumination/regurgitation, psychogenic vomiting (Gravestock, 2000), faddy attitudes toward food, and selective food refusal (Gravestock, 2000, Psychiatrists, 2001). The core cognitive and perceptual distortion accompanying anorexia and bulimia are difficult to be investigated in moderate-to profound ID. Indeed, according to DC-LD definitions disturbed body image and also hormonal

dysfunctions are not considered among the diagnostic criteria in this population. By the contrary, the compensatory behavior of self-vomiting assumes a crucial relevance in both. Similarly, compulsive eating is commonly shared by bulimia and BED, assuming in BED severer levels. Other peculiarities of eating are common in BED, such as fast and eager eating, "bolting", stealing or hiding food (Hove, 2004). Obviously, the physical hallmark is usually represented by various degrees of obesity.

Post-Traumatic Stress Disorder

PwID have been found more likely to experience traumatic events comparing to the general population, 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 and related disorders (Tomasulo and Razza, 2007). Language deficit and impairment in identification or description of their experiences and emotional state make it difficult to identify PTSD in individuals with ID. Studies found that traumatic experience in this population often manifests itself with disorganized or agitated behavior, while re-experiencing the trauma takes the form of behavioral acting out of traumatic experiences, self-injurious behavior, nightmares without recognizable trauma-specific content that can appear as symptoms of psychosis (Fletcher et al., 2007, Mevissen and de Jongh, 2011).

1.5.3.2 Clinical features of psychiatric disorders in low-functioning autism spectrum disorders

Psychiatric comorbidities are common in ASD and frequently lead to further associated impairment. Diagnosis of co-occurrent PDs is often challenging due to several difficulties including the core symptoms of ASD themselves, communication deficits, atypical presentation of psychiatric symptoms, and scarcity of standardised diagnostic tools (Vannucchi et al., 2014a). Furthermore, the clinical manifestations of ASD often overlap with the symptoms of other disorders; thus, it can be difficult distinguishing between them (Matson and Sturmey, 2011, Underwood et al., 2015). Finally, the superposition of some PDs on the basal neurodevelopmental disorder may arise clinical pictures easily confused as other clinical conditions in standard psychiatric settings because of the pathoplastic effect of ASD on the secondary condition.

Anxiety disorders

Clinically significant anxiety is common in individuals with ASD and is related to increased psychosocial, and familial impairment (Nadeau et al., 2011). Several features of autistic persons may make them particularly prone to anxiety-driven reactions. For example, insistence on sameness and adhesion to routine are considered core features in most patients. Environmental perturbations or more substantial changes (for example, change of living arrangement, transition to different educational settings, loss of significant others) may cause dramatic reactions as well as they can act as triggers for a full-blown anxiety disorder.

People with ASD and comorbid anxiety may show increased ritualistic behaviors and PBs, even self-injury and aggressiveness toward object or others, as well as tantrums and fugues (Davis et al., 2012). The difficulties in expressing worry and fear challenge the diagnosis and such behavioral manifestations may suffer of both

diagnostic overshadowing or misdiagnosis. For example, agitation may be misattributed to manic states or other residual and generic diagnoses.

Social anxiety disorder is more likely among high-functioning ASD individuals than in low-functioning. In this population social anxiety and ASD may have areas of differential diagnosis. Contrary to the popular opinion, in spite of their impaired social skills, most persons with ASD strongly desire social interactions but struggle with them. Negative experiences with others and actual ostracism by peers may be the ground of avoidant behaviors and social withdrawal. In spite of the fear of appearing inappropriate in social contexts, neurotypical social phobic patients are usually adequate; ASD is instead associated to social awkwardness up to bizarre and inappropriate behaviors (Bejerot et al., 2014).

Obsessive-Compulsive Disorder

Obsessive thoughts and stereotypical behaviors are commonly observed in ASD and overlap with OCD in the symptomatic profile (Ivarsson and Melin, 2008). Thus, it can be difficult to distinguish symptoms that are related to a comorbid OCD, particularly in people with lower functioning levels. Some studies have indicated that repetitive thoughts and autistic behaviors differ from those of OCD (Cadman et al., 2015, Ruzzano et al., 2015). In OCD, typical obsessive themes include worries about germs, harm to self or others, pathological doubt, and obsessive preoccupations with moral, religious or sexual themes. Therefore, typical compulsions include ritualized washing, checking, ordering, apologizing, or mental rituals such as counting or praying. People with ASD may perform repetitive or ritualistic behaviors such as ordering, arranging, counting, or touching/tapping resembling compulsive behaviors (McDougle et al., 1995). These behaviors are more likely complex stereotypies than compulsions. Indeed, defence psychism is not present in these cases: autistic subjects with stereotypic rituals are not aware or preoccupied about the reason behind their ritualized behaviors. Rather, ritualized behaviors 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. In this perspective, someone can argue the substantial absence of obsessions and ego-dystonia. However, even in low-functioning ASD, OCD may be present, usually with absence of insight. Despite DSM-5 separate OCD by anxiety disorders, the anxiety underpinning and accompanying rituals is a meaningful hallmark of co-occurring OCD in low-functioning ASD. The rituals tend to become more pervasive with time, are not related to environmental stimuli, as for example changes of routines which can instead elicit stereotypies. OCD rituals are always absent or minimal in unknown context, but are completely absorbing in familiar settings. When the person is prevented to act or complete the ritual may remain on look out to the moment of resume it or may blow up in severe rage. The attenuation of symptoms under behavioral and antidepressant treatments is an *ex adiuvantibus* criterion for the co-occurrence of OCD in ASD.

Psychotic disorders

There is a broad overlap between ASD and schizophrenia spectrum disorders (King and Lord, 2011) not only including the phenomenology of the disorders but also commonly shared cognitive, neurobiological and genetic underpinnings. Transition into adulthood and exposure to stressful events are related to the onset of brief psychotic episodes in adults with ASD. Furthermore, psychotic symptoms may be in most cases the hallmark of an underlying mood disorder or a schizoaffective disorder (Underwood et al., 2015).

As discuss for the diagnosis of psychosis in PwID, it seems important to distinguish psychotic-like from psychotic symptoms. Emotional reciprocity deficits may condition misattribution of significance to interpersonal interactions resembling referential ideas. Sensory issues in non-verbal subjects may be misconceived as perceptual disturbances. Stereotyped or unusual behaviors may seem bizarre and odd. When depression or mania occur, these symptoms may result intensified and they be misinterpreted as psychotic symptoms and the misdiagnosis of schizophrenia can be made rather than mood disorders (Skeppar et al., 2013). On the other hand, the co-occurrence of hallucinations and delusions as well as negative symptoms of schizophrenia may actually be recognized in ASD persons along with the typical deteriorative course of schizophrenia or the episodic nature of MDs. The pervasiveness of symptoms, the association with alarm signs, the fluctuations in intensity and the influence of hallucinations and delusions on behavior may be signs of true psychosis in ASD.

It can be hypothesized that when negative symptoms prevail a diagnosis of schizophrenia is likely in ASD persons (Kästner et al., 2015), whereas the prevalence of productive clinical picture is suggestive of a MDs, mainly mania (Larson et al., 2017).

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). Autism and eating disorders, especially anorexia nervosa, have common features concerning cognitive style and behaviors (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 difficulty detected in people with ASD especially for their difficulties in defining their inner psychic state (Mehtar and Mukaddes, 2011). The diagnosis of PTSD requires 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.

1.6 DEPRESSIVE AND BIPOLAR DISORDERS IN INTELLECTUAL DISABILITY AND LOW-FUNCTIONING AUTISM SPECTRUM DISORDERS

1.6.1 GENERAL ISSUES AND DIAGNOSIS

Affective disorders in PwID and low-functioning ASD (LF-ASD) are an understudied area and the available epidemiologic and clinical data raise uncertainties. In the previous chapter the complex issues regarding the psychiatric diagnostic process and the substantial inadequacy ang generalizability of current standardized diagnostic criteria were discussed. The history and the issue of diagnosing MDs in intellectually disabled persons followed the same pathway. The first descriptions of melancholia and mania in mentally retarded date back to the 19th century and some authors identified ID as a risk factor for the development of depression (Sikabofori and Iyer, 2012). Despite these observations, almost another century was needed to overcome the prominent concerns regarding the occurrence of clinical affective disorders in ID, especially in persons with severe impairment (Earl, 1961). Some authors described development and features of depression and mania in mental retardation as well as the response to lithium (Hasan and Mooney, 1979, Naylor et al., 1974, Reid, 1972). Therefore, in the '80s Sovner and Hurley (Sovner and Hurley, 1983) stated that individuals with ID may experience the full range of affective disorders and systematically conceptualized depression and BD in ID, also suggesting the utility of special "symptom criteria". Later, this concept was resumed and Sovner (Sovner and Pary, 1993) produced an adaptation of DSM criteria for BD in ID, providing articulated examples and descriptions.

Most of the available literature in this field regards depression rather than mania and BD. *Depression* occurs in ID and LF-ASD more frequently than in the general population (Cooper et al., 2018, Hurley, 2006, Janowsky and Davis, 2005). Although the demonstrated validity and reliability of the diagnosis of MDs according to standardized criteria in BIF and mild ID, the diagnosis of depression _as well as mania_ may result more challenging in persons with greater cognitive and communication impairment. This aspect relies the diagnosis mostly on informant reports, in contrast with usual practice requiring a deep investigation of internal states as essential dimension of mood syndromes (Charlot et al., 2007b, Courchesne et al., 2001, Hurley, 2007). Individuals with ID may not be able to describe their own emotions accurately or reliably, and this clue does not regard only severely impaired persons but also verbal individuals with mild ID (Bertelli et al., 2015, Costello and Bouras, 2006, Ross and Oliver, 2003). This is a general issue for the diagnosis of any PD in ID and LF-ASD, but it becomes an essential point for especially diagnosing depression. The cognitive impairment may also reduce the ability to understand and report complex concepts and feelings such as guilt, worthlessness, diminished ability to think, but also thoughts of death and suicidal ideation. These symptoms all represent individual criteria for the diagnosis of the MDE: it is expectable that the rigid application of full standardized criteria referring to these concepts and using the same cut-off for the minimum number of symptoms designed for neurotypical individuals, may be result inadequate (Cooper and Collacott, 1996, Davis et al., 1997a, Janowsky and Davis, 2005, Smiley and Cooper, 2003). Instead, a more pragmatic application of standardized criteria may, to some extent, overcome this issue (Marston et al., 1997, Meins, 1995).

The reliability of the informant is the other great issue to deal with in diagnosing depression. In ID the presentation of internalizing non-disruptive symptoms may be overlooked by care-givers and observers who usually over-report externalizing symptoms such as irritability, over-reactivity, agitation and behavioral correlates, mostly aggressiveness toward self or others (Charlot et al., 1993, Marston et al., 1997, Moss et al., 1998). Those PBs are the first reason to seek treatment for ID and LF-ASD persons (Hurley, 2007). The overlook of other signs and symptoms suggesting a depressive underpinning is a major cause of inaccuracy in the assessment of MDs: the subsequent implication is the choice of behavioral and pharmacological treatments focused on the extinction of the PB rather than to treat the underlying disorder. This is also the reason why a psychiatric diagnosis only based on behavioral equivalents as unique reference of psychopathology is not recommended (Fletcher et al., 2016). PBs are intended to be possible "state dependent" features of depression but they are not diagnostically specific to depression (Charlot, 2005, Sturmey et al., 2010, Tsiouris et al., 2003). Some authors had an extreme position at this regard, down-grading the relevance and validity of behavioral equivalents (Ross and Oliver, 2003). However, some research demonstrated that DSM diagnostic criteria and depressive equivalents were both related to the diagnosis of depression in intellectually disabled persons, with also a significant relationship among the diagnosis of depression, depressive equivalents and PBs likewise aggression and self-injury (Langlois and Martin, 2008).

The minimal modification of existing guidelines and criteria accounting for the pathoplastic effect of the neurodevelopmental level on the presentation of depression is the most accepted approach in the scientific community (Cicchetti and Toth, 2009).

The use of multidisciplinary assessment, multiple informants, and longer time to observe the patient and collect information reduce the diagnostic biases. To avoid or reduce the interpretations of the informants, it should be preferred the use of tools providing detailed descriptions of the appearance and behavior of the patient rather than mere checklists (Fletcher et al., 2016, Hayes et al., 2011, Ross and Oliver, 2003). The clinician and the assessing instruments should account for the *baseline exaggeration* of symptoms and behaviors, carefully considering the baseline developmental level and behavioral repertoire of the individual. This helps to both avoid automatic attribution of behaviors mostly PBs to psychopathology, as well as the overshadowing of psychopathological ground, leading to over- (Davis et al., 1997a, Holden and Gitlesen, 2004) and underdiagnosis (McBrien, 2003), respectively. Targeted questions regarding clinical features but also age at onset of symptoms and PBs, variations over time, clinical course, treatment-emergent conditions, environmental variables, life-events and family history for MDs are important clinical validators for the diagnosis of depression and MDs in general (Hegerl et al., 2008). The exclusion of other sources of distress is likewise important: PBs may be underlie by a variety of environmental stressors but it is crucial to exclude co-occurring medical illnesses including urinary retention and infections, gastric reflux, constipation, pain, seizures and others (Charlot et al., 2011, Espie et al., 2003, Kennedy et al., 2007, Kwok and Cheung, 2007). Side effects of medications, namely antipsychotics, may fully mimicry the clinical picture of depression (Sovner and Hurley, 1983): reduced reactivity and motivations, psychomotor retardation or agitation and

restlessness may commonly be caused by these compounds and, in this population, it is particularly difficult to identify them as extrapyramidal symptoms such as flattening, parkinsonism and akathisia.

The proposal for substituting or integrating standardized criteria with behavioral equivalents raises from a documented tendency to underdiagnosis, mostly related to difficulties in obtaining reliable self-reports from verbally impaired patients. On the other hand, the application of behavioral equivalents has been argued to be misleading toward over-inclusiveness (McBrien, 2003).

The adaptation of DSM-IV-TR criteria produced by the National Association for the Dually Diagnosed (NADD) in collaboration with the APA, Diagnostic Manual – Intellectual Disability (DM-ID), later revised to after DSM-5 was published (DM-ID-2), according to some part of the literature, provided only minor changes to the standard criteria for depression (Charlot et al., 2007b). The most important suggestions of the DM-ID and DM-ID-2 were that:

1. In PwID irritability may present frequently as or more than sadness (Charlot, 1997, Davis et al., 1997b), thus irritable mood has to be considered an equivalent of depressive mood and not a counterpolar symptom. Similarly, psychomotor agitation seems to be a feature of depression more commonly found in ID than in the general population.
2. The cut-off for the minimum number of symptoms for MDE was at least four symptoms and not five.
3. Specific emphasis were given to the change of functioning, also including not only the new onset but also the worsening of 'agitated behaviors' such as assaults, self-injury, disruptive or destructive behaviors, as well as stereotypes and ritualistic behaviors. Some descriptions and examples were provided in order to depict how symptoms may be inflected in ID. For example, reduced appetite may present as refusing meals, or exhibiting agitated behaviors at meal times such as throwing food and screaming when meals arrive.

The Royal College of Psychiatrists in the DC-LD suggested modifications to ICD-10 criteria for depression, specifically addressing the diagnostic difficulties in persons with moderate to profound ID. DC-LD also attempted to provide a legitimate framework of PBs according to a hierarchical approach: clear instructions regarding organic disorders and behavioral phenotypes. The adaptation of the symptomatic criteria was somehow more pragmatic than in DM-ID: it provided the replacement of some self-report items with observable items (Smiley and Cooper, 2003). Moreover, the DC-LD suggested for these subpopulations the elimination of cognitive-based symptoms (feelings of guilt and unworthiness, pessimistic views about the future and ideas of self-harm) and in place of the inclusion symptoms, behavior-based, such as the increase of specific maladaptive behaviors or somatic symptoms concurrent with mood and psychomotor symptoms of depression _but also mania_.

Similar considerations are applicable to *mania* too, although the literature is far less extended than for depression. Some authors suggested a particular relevance of the developmental appropriateness: in fact, there are some evidence suggesting that not only the atypicality of the single episode but also the course of BD may resemble the features reported in bipolar young children (Rutter, 2011). The detection of full counterpolar episodes as well as mood and symptomatic fluctuations across time is the core diagnostic feature of BD. These aspects of atypicality and often stormy nature of the course of the illness in ID patients represent a major

hamper to the diagnosis. This suggestion is confirmed by the observations that BD is commonly misdiagnosed in ID because of difficulties in eliciting histories of mood change and tendency toward an overemphasis on psychotic and pseudo-organic symptoms (McCracken and Diamond, 1998). By the contrary, other authors concerned mania to be over-diagnosed because hyperactivity and excitement are common in these individuals (Einfeld, 1992), often in the form of hyperkinesia mixed to impulsivity as it has been extensively historically associated to the so-called minimal brain damage, the forerunner of current ADHD.

There are data actually indicating that the presentation of BD in PwID may be distinctly different from the general population (Ruedrich, 1993), not only because the cross-sectional manifestations may be atypical, but also because of it frequently presents a chronic, or rapid cycling course (King, 2000, Sovner, 1989, Wieseler et al., 1988). Both chronicity and rapid cycling are associated to worse outcome and reduced response to standard treatments as in average IQ persons (King, 2000).

From a symptomatic perspective, mania in individuals with ID may present similar diagnostic issues as depression., mostly in individuals with moderate-to-profound ID. Data from case descriptions and retrospective chart reviews, suggested that irritability and dysphoria may be equally or more common than euphoria (Cain et al., 2003). Comparing to other psychopathological ID groups, BD-ID patients also may be more likely to exhibit higher number and severity of non-mood symptoms such as increased energy, decreased sleep, disturbances of speech, distractibility, impulsivity and increased engaging in pleasurable activity, but also increased self-esteem. These symptoms taken together, are all suggestive of mania and fit with standardized criteria, in fact no adaptations have been provided in the DM-ID-2 to the symptomatic criteria for both mania and hypomania, and it only provided descriptions and explanations of the symptoms. However, symptoms may also have peculiar presentations which make the diagnosis less clear in clinical practice: for example, when language is absent and severe motor disability co-occur, altered speech might be replaced by increased production and tonality of vocalizing and screaming. Pressured speech might be rather represented by augmented intensity of social interactions often assuming the aspect of disturbing behaviors. Indeed, a wide range challenging and maladaptive behaviors have been reported (Cain et al., 2003). The increase of self-esteem can be hard to detect, because of the cognitive skills required to be correctly explored. Moreover, pseudological thinking is common in intellectually disabled persons and not necessarily indicative of excitement. Cyclical behavioral deterioration might be in some cases the prominent sign of the disorder (Fletcher et al., 2016).

The most challenging diagnostic issue may be the differentiation between mania and hypomania, BDI and BDII. That there are no studies regarding the phenomenology of BDII in PwID does not help in solving this issue. The differences regard by definition the severity of the overall clinical picture, reflected in the measures required to treat the syndrome and prevent disruptive consequences. For hypomania the change from usual functioning has to be unequivocal and observable by others but not so severe to require hard measures as in the case of mania. Such a difference is much vaguer in clinical practice, not only between mania and hypomania but also between hypomania and normal functioning. In most cases self-reported symptoms are not available and the diagnosis is almost exclusively based on the observation of an informant. Subsequently, this fact

reduces the reliability of this criterion. Moreover, with some differences across Countries (Wu et al., 2013), the tendency toward hospitalizations of intellectually disabled persons in acute psychiatric units appears less likely than for average IQ persons: they are more frequently managed where they live, mostly if they live in residencies. The presence of psychotic symptoms is indicative of mania. Not considering the difficulties of diagnosis psychosis in ID and especially LF-ASD, the presence of psychosis may hamper the differential diagnosis with schizophrenia and other schizophrenia spectrum disorders. The prominence of neurovegetative symptoms, agitation, and psychotic symptoms during the excitement phase and the long-lasting mild course of depression, with prominence of anergia ad motivational deficits may easily lead the clinician to a diagnosis of schizophrenia a (Mazzone et al., 2012).

In conclusion, it is important to understand that, although current diagnostic criteria and psychiatric diagnostic process conducted as usual my result inadequate to correctly frame MDs in ID and LF- ASD, behavioral equivalents alone are not sufficient to make a diagnosis. A compromise position would be that behavioral equivalents could be operationalized as additional descriptive alternatives to the symptomatic criteria for MDs provided by DSM and ICD: a mixed approach providing the use of additional clear, behavior-based descriptions of possible manifestations of each DSM-5 or ICD-11 criterion is likely to better ensure the highest reliability in assessing and diagnosing these disorders in this peculiar population (Clarke and Gomez 1999, Fletcher et al., 2016).

1.6.2 EPIDEMIOLOGY

The issues regarding the diagnosis and classifications of affective disorders in ID necessarily affect epidemiological data. According to different assessing methods, sampling and diagnostic criteria, MDs have been considered underrepresented, equal, or overrepresented comparing to the rates found for the general population (Janowsky et al., 2003). Usually, clinical studies suffer for large referral bias: it is expectable that the rates of PDs, namely MDs, are higher in clinical facilities, ambulatories and rehabilitative centers because it is more probable to find mental health issues among individuals needing intensive care. This aspect creates a bias especially for persons with BIF and mild ID, usually not entering psychiatric or psychological assistance pathways when not problematic. Equally, data derived from populations living in residencies may lead to overestimation of the rates: young persons with severe and profound ID are usually managed at home in absence of maladaptive behaviors. On the other hand, large population-based studies, in which the diagnosis is relied on the mere application of standardized criteria rather than a complete and complex assessment by trained professionals, may suffer for reduced diagnostic sensitivity and may lead to overestimation of the impact of MDs in this population, mostly in persons with moderate-to-profound ID.

Depressive Disorders

Depression is common among ID persons (Cooper et al., 2018), although some authors found different results. For example, in a dated study on a sample of PwID, with mainly severe and profound ID, the point prevalence of depression resulted 0% in contrast to higher incidences of those with schizophrenia and anxiety disorders

(Linaker and Nitter, 1990). In the same sample the authors suggested that this datum was coherent with the very low use of antidepressants in both institutionalized and non-institutionalized intellectually disabled persons comparing to the general population (3% vs. 9%, respectively) (Rinck, 1998). In contrast, although the general paucity of reliable data, there is a certain agreement that PwID may show an increased vulnerability to depression than the general population (Cooper et al., 2018): for example, mild ID teenagers have shown a four-fold increase of the risk for developing depression and other affective disorders in the following years (Richards et al., 2001) and the severity of depressive symptoms is higher among adolescents with ID comparing to their typical peers (Heiman, 2001).

In the milestone population-based study conducted by Cooper and her colleagues (Cooper et al., 2007d, Cooper et al., 2007c) they found depression to be prevalent in the 4.9% of the overall sample of more than a thousand of PwID. This prevalence relied on the DC-LD criteria for depression. Differential point prevalence according to the ID level was 3.8% in mild ID, 4.4% in moderate ID, 4.6% in severe ID and 2.2.% in profound ID. In this large study, depression was associated to female gender and preceding life events, whereas occupational status and sensory impairment did not emerge as risk factors. These data were obtained using adapted criteria. The same sample evaluated with DSM-IV-TR criteria reported a prevalence of affective disorders of 1.1%, almost five-fold smaller (Cooper et al., 2007a). In the 2-year follow-up of the Cooper's study, the 2-years incidence was 6.1% according to the clinical diagnosis, 1.5% using DSM criteria. In a replication of this study, Cooper substantially confirmed these results (Cooper et al., 2018), comparing these rates to those of the general population, reporting 2.9% rate for DDs (Lehtinen et al., 2005).

In psychiatric settings, the rates are markedly higher with lower amplitude of the differences between the application of standardized and adapted criteria: for example, in a sample recruited in a psychiatric admission unit the prevalence of MDE was 44% and 59% with DSM criteria and a specific assessing instrument for intellectually disabled persons (MASS), respectively (Charlot et al., 2007b).

It seems that depression in PwID may be more enduring than in typically developed persons, maybe because it is likely undertreated (Cooper et al., 2018).

Bipolar disorders

As claimed in DM-ID-2, although the literature provided descriptions of BD in PwID, reliable systematic, controlled studies assessing the prevalence of BDs, not only BDI, according to DSM-5 criteria are lacking. Some earlier studies reported BD ranging from 0.9% to 4.8% in the intellectually disabled population (Reid, 1972, Ruedrich, 1993). The variability of rates depended on criteria as well documented by a more recent study investigating different diagnostic approaches (Cain et al., 2003): of the 68 ID patients clinically diagnosed with BD, only around the half (36) met the DSM criteria. In a community-based study also accounting for BDII, the prevalence of mania and hypomania together reached the 2.2.% (Deb et al., 2001a). In the studies by Cooper and colleagues (Cooper et al., 2018), mania showed considerably higher incidence rates comparing to general population, reaching 1.1%. Incidence rates for bipolar depression are comparable. Interestingly, the standardized incidence ratio (SIR) for the first episode of mania was 41.5 and grew to 52.7 excluding persons

with Down's Syndrome (who had 0% incidence for BD). The SIR for a bipolar affective episode was 2.35 and 2.54 according to clinical and DC-LD diagnoses, respectively, comparing to 1.19 and 1.07 for depression. These results are very important as they can be interpreted as the consequence of poorly diagnosed BD in spite of its clinical relevance in this population.

According to this perspective it is expectable that prevalence rates in clinical populations may result much higher. For example, the rates of BD in ASD children and adolescents, including both high and low-functioning, has been found to range between 2.3 and 10.4% (Rosenberg et al., 2011). In pediatric populations of LF-ASD the prevalence of BD was found around 6% (Rosenberg et al., 2011), expectably growing among adults, given that the onset peak is estimated during the transition from adolescence into adulthood.

There is a substantial paucity of studies about the occurrence of BD in first-degree relatives of persons with ID, whereas the familial relationship between BD and ASD seems more replicated by studies (Bolton et al., 1998, Piven and Palmer, 1999). Among ASD persons, a positive family history for affective disorders can be found in the 17% and 13% of the family members of Autistic and Asperger subjects, respectively (Gillberg and Gillberg, 1989). Several studies reported higher prevalence of depression and BD among ASD patients' relatives compared to family members of children with other types of disabilities (Bolton et al., 1998, Lajiness-O'Neill and Menard, 2008, Piven et al., 1991). This relationship seems to be stronger for high functioning autism (DeLong and Aldershof, 1987, DeLong, 2004), whatever identifiable in LF-ASD too. The majority of the studies on psychiatric morbidity of ASD patients' parents showed that MDs onset usually precedes the birth of the offspring. This observation suggests the prominence of biological and genetic underpinnings in MDs among relatives of ASD patients, particularly HFA; on the contrary, a reactive component linked to the stress of care-giving a disabled child might have less pathogenetic weight (Bolton et al., 1998, Cohen and Tsiouris, 2006). A large Swedish study, including 988 couples of mother and child, examined the potential association between maternal history of mental disorders and phenotypes of ASD (Vasa et al., 2012). It was found a significantly higher prevalence of both depression (47.1% vs 39.1%) and BD (10.1% vs 6.2%) in mothers of high functioning ASD probands than in the mothers of LF-ASD children. Noteworthy, both the rates for high ang low functioning are significantly higher than those of the general population. On the other hand, other studies found the co-occurrence of ID in ASD to be associated to a risk of having a parent with BD almost equal to the general population (OR 1.1), whereas it increases up to 1.7 in ASD without ID. On the other hand, the risk of ASD is higher (O.R. 2.5) among the siblings of bipolar patients (Sullivan et al., 2012).

There are no data accounting for the differential prevalence of different BDs and most studies regarded BDI or did not provide a subcategorization. Thus, no data are available about the overall bipolar spectrum including cyclothymic disorder. Moreover, in our knowledge only few studies explored the epidemiological characteristics of mixed states in PwID, although some experts suggested that they are much more common and characterizing MDs presentation in ID, as well as rapid cycling (Reid et al., 1981, Ruedrich, 1993). The incidence of mixed affective episode according to different diagnostic criteria resulted 0.2% in the study by Cooper and colleagues (Cooper et al., 2018), while in a chart review study in young PwID, the prevalence of mixed affective symptoms was 4.5% (Felstrom et al., 2005). Further information may be derived in specialistic

clinical setting. Only one study examined the differential prevalence of pure manic and mixed manic episodes in ID. It was a retrospective chart review of 80 adolescent inpatients admitted in hospital for acute manic or mixed episode. The study provided the IQ evaluation for all the patients and found that the 21.3% of them ha ID (Brunelle et al., 2009). The comparison of ID and non-ID subgroups evidenced that ID adolescents accounted for the 10% of the overall mixed manic episodes and the 29% of those with pure manic features (Brunelle et al., 2009). It has also been reported that a significant proportion of patients with mixed affective episodes can present with catatonic symptoms (Braunig et al., 1998, Kruger et al., 2003). Interestingly, acute bipolar inpatients have been reported to suffer for inequalities in treatments. Contrary to the expectations and to data claiming PwID to be usually overtreated, when correctly identified they may receive lower dosage of appropriate medications comparing to their average IQ peers. This attitude implies much longer duration of hospitalizations, incomplete symptom resolution and long-lasting functional impairment (Wu et al., 2013).

Epidemiological data about rapid cycling BD in PwID are still inconclusive but suggestive. In 1999 a systematic literature review was conducted on this topic (Vanstraelen and Tyrer, 1999). The authors found 14 papers including a total of 40 intellectually disabled persons with BD evaluated. Contrary to the literature about rapid cycling in typically developed persons, in PwID rapid cycles are not associated to female gender but are equally represented in male and females. Rapid cycling has also been associated to earlier onset of PDs in general and specifically BD and it seemed that over one-third of rapid cyclers started with rapid cycling. Regarding the heritability of BD, the authors reported that the majority of patients with comorbid ID and rapid cycling BD had family history for affective disorders and this relationship resulted surprisingly more significant for those persons with higher cognitive impairment. No organic pathologies were specifically associated to rapid cycling.

1.6.3 CLINICAL FEATURES

Depressive Disorders

There is a considerable debate about the clinical characteristics of depression in PwID and LF-ASD. To summarize, individuals with mild ID may show classic features fitting with standardized diagnostic criteria, whereas those with moderate-to-severe ID may present depression in different forms and with atypical features (McBrien, 2003). According to the idea that persons with ID show peculiar neurovegetative vulnerability and psychomotor involvement during depression, symptoms as psychomotor retardation, apathy, withdrawal, appetite and sleep disturbances, but also loss of daily skills and reduction in the cognitive performance, are common features across the ID levels (Davis et al., 1997a). In severer cases ID are also very common behavioral disturbances associated to depression, namely aggressiveness, self-injury, crying, screaming and temper tantrums (Cooper and Collacott, 1996, Marston et al., 1997).

The onset and risk factors for DDs in PwID are similar to those in the general population. The onset is usually between late adolescence and early adulthood (Tonge and Einfeld, 2003), whereas late onset, for example around the fifth decade, requires careful consideration and long-term follow-up to draw conclusions because a psychiatric presentation could probably be the first manifestation of neurodegenerative processes. Some

subpopulations are particularly vulnerable: it is well-known the increased risk for Alzheimer-type dementia in persons with Down's syndrome since the fourth decade of life. Environmental stressor immediately preceding the onset, at least for the first unipolar depressive episodes, and pre-existing problem behaviors are risk factors for the development of unipolar depression in adults with ID (Cooper et al., 2018). There is no agreement regarding the influence of heritability, gender and socio-occupational status.

The diagnosis of MDD would require a recurrent pattern with multiple episodes. Comparing to bipolar depression, unipolar one has been found to show less abrupt development (Hegerl et al., 2008). There are no systematic data regarding seasonality of recurrences but in clinical practice is common to find recrudescence of depressive and anxiety symptoms with seasonal pattern. In most cases, the intensity of seasonal symptoms does not achieve the severity of full MDE but can be softly impairing anyway.

There are no systematic and population-based studies addressing persistent depressive disorder, formerly dysthymia. The few reports regarding it (Jancar and Gunaratne, 1994, Puigh-Antich and Chambers, 1983), described clinical pictures similar to those in average IQ persons. Symptoms are at most mild but long-lasting and interfering with the functioning, especially with social adaptation. The mood can be depressed or irritable, energies are usually poor as well as concentration and volition, thus the person engage with daily activities with difficulties. In PwID these difficulties may assume more easily the behavioral features of malingering, but attention-seeking behaviors are frequently found. In mild ID individuals, chronic feelings of guilt and low self-esteem co-occurring with generalized anxiety are associated to lamenting. Persistent depressive disorder in moderate-to-profound ID represents a diagnostic challenge. With the exception of cognitive symptoms usually poorly evaluable in this population, there is a large overlapping area with negative symptoms of chronic schizophrenia spectrum disorders but also with iatrogenic affective flattening and impairment of hedonic-motivational pattern due to long-term use of antipsychotics.

As for mood disorders in individuals with typical neurodevelopment, the phenomenology of depression can be sectioned exploring the three fundamental dimensions involving affectivity: mood, activity and behavior, cognition and perception.

1. Mood

The quality of depressive mood is similar in mild ID as in average IQ individuals. Independently from the IQ level, the hallmark of depression is that depressed affect varies little day to day and is poorly responsive to circumstances (Sikabofori and Iyer, 2012). As in the general population, diurnal variations of intensity or prominence of different symptoms are possible in ID too. However, sad pervasive affect may be prominent only in a proportion of patients: in fact, irritability, dysphoric mood (Lowry, 1998, Tsiouris et al., 2003) and mood lability (Charlot et al., 1993) may be as common as sadness or rapidly alternating one each other. This is coherent with the developmental perspective which parallels depression in intellectually disabled individuals to that in typically developed young children (Cicchetti and Toth, 2009). Irritability and reactivity usually increase the sensitivity to frustration. The person with good verbal skills may report feelings of sadness or rage, may appear tearful and demanding. However, vague and highly variable complaints are more common,

mostly about somatic symptoms (Charlot, 1997, Charlot et al., 1993, Lowry, 1998, Rojahn et al., 1993, Tsiouris et al., 2003).

Loss of interest, reduced emotional response and anhedonia are core features of depression. They are constructs very difficult to be described by persons with low cognitive and verbal skills, but often there are behaviors that can be interpreted as their correlates. For example, a person with mild ID could not be able to tell that is not able to "feel feelings" or that he/she lost the will or the pleasure to do things: thus, when asked to do or to choose something, he or she could only shows renunciatory attitudes and says "I don' care" (Fletcher et al., 2016). At a first sight these could be interpreted as laziness or, when repeating over time, as a tendency to become easily tired of activities. In severer depression, withdrawn and social avoidance may become prominent aspects in the clinical picture (Cooper and Collacott, 1996). In persons with severe/profound ID, the combination of irritability and altered hedonic-motivational pattern often represents the underpin of PBs during depression. In fact, PwID and depression may display oppositional-defiant behaviors, tantrums or aggressiveness toward objects or others in order to escape care-givers' requests, stimulations or the participation to activities in which they have no longer interest (Lowry and Sovner, 1992).

Finally, anxiety and its behavioral correlates are also frequent in depressive PwID (Charlot et al., 2007a, Hurley et al., 2003, Marston et al., 1997). Excessive preoccupations, fears and thoughts regarding health and safety, physiological signs of anxiety may occasionally be reported by the patient, but an effort has sometimes to be done to frame eventual odd and peculiar interpretations. An intellectually disabled person with panic attacks or anxiety crises could simply repeat "I don't want to go to the doctor", "no more, no more". PwID may also have difficulties in identifying that chest pain is related to tachycardia and palpitations, for example, and may generally talk about stomachache. Neurovegetative symptoms are equally present in mild as in moderate-to-profound ID, may be related to environmental stimuli or spontaneous and, when anxiety is a feature of depression, recurrent diurnal variations may be identified. Neurovegetative signs, for example sweating, trembling, gasping for air or frantic breath, coughing, vomiting, diarrhea and reduced urinary and fecal continence, can be associated to crying, screaming, running around or away, restlessness or grabbing to someone. In some cases, anxious ID patients may become strongly demanding and may act self-injury in order to obtain the attention of the reference adult. There are also other symptoms equivalents possibly related to anxiety during depression. In PwID and LF-ASD, stereotypies, involuntary movement, repetitiveness, and also OCD spectrums symptoms including environment hyper-control, rituals, but also skin picking and tricothillomania, can increase during depression and are usually accompanied by anxiety (Charlot et al., 2007a, Hurley et al., 2003, Marston et al., 1997).

2. Activity and Behavior

Lack of energy is strictly related with anhedonia and altered motivational pattern. Various degrees of fatigue, asthenia, lethargy, but also psychomotor retardation may implicate noncompliance and unresponsiveness (Matson et al., 1999). The global aspect of the person and the mimic are coherent with mood: the depressive patient usually shows under-reactivity of facial expression to environmental stimuli, smiling is difficult to be elicited, the facial expression can oscillate from flatness to sadness, tearfulness, or it can express rage and

aversion. The person can be oppositional toward interaction, isolated, and a loss of confidence with persons and environment can be the final result. When speech is present, it is reduced in volume and content, in some cases the person refuses to talk and answer. Mutism is not uncommon. In non-verbal patients reduced interactions even with familiar people, scarce research of interpersonal contact, avoidance of social circumstances can be considered behavioral equivalents of these aspects. A reduction in self-care is very common and the attempt of the care-giver to help the person providing self-hygiene or wearing clean clothes is one of the commonest triggers or antecedents for tempers and aggressions.

Psychomotor agitation seems to be twice as common as retardation in PwID (Tsiouris, 2001). Psychomotor agitation is easy to be detect because of its disruptive nature. Rather, it is often the symptom which clinicians and informants focus on, and it may unfortunately mislead diagnosis and management. Restlessness, running away, sudden screaming, vocalizing or disorganized and purposeless motor activity are behavioral signs. Agitation is often associated to PBs, even if they are not specific as extensively discussed. By no means, most individuals show a combination of both psychomotor retardation and agitation, rapidly shifting from one to the other, often in response to a demanding environment (Charlot, 1997, Charlot et al., 1993, Meins, 1995) .

In severe and profound ID as well as in LF-ASD it can be very difficult to distinguish a "simple" combination of these psychomotor symptoms from catatonia. In some cases, rapidly alternating counterpolar psychomotor symptoms would configure a mixed state, for example agitated depression. When changes are extreme, a diagnosis of catatonia should be considered. The classical symptoms of catatonia, for example posturing, grimaces, motor rigidity, waxy flexibility, stereotypies and echolalia may pertain to core features of ASD or may be not identifiable in persons with severe motor disability, for example in severe cerebral palsy and when severe spasticity is present. This is not a moot point, especially considering the complex interrelationship existing between catatonia, affective disorders and some PBs. Indeed, some authors and expert clinicians hypothesized severe self-injury with recurring pattern to belong to catatonia in depressive and bipolar ASD children (Fink et al., 2006). In most cases, standard psychopharmacological treatments fail or worsen symptoms, whereas electroconvulsive therapy has been demonstrated to be effective (Wachtel et al., 2018).

Sleep and appetite disturbances have been found to be markers of depression in PwID and have to be considered even more important hallmarks in severe and profound ID (Tsiouris, 2001). Insomnia, nightmares, multiple awakenings associated with screaming, fear and attention-seeking behavior have been documented. Less is known about the presence of diurnal hypersomnia, which is commonly found in clinical practice. However, hypersomnia may be easily due to sedation as side effects of medications used to treat insomnia or disruptive behavioral disturbances. Similar considerations can be drawn for the alterations of appetite and weight during depression: hyporexia, refuse to eat, increase of pre-existing selectivity for foods are common symptoms (Mayville et al., 2005). By the contrary, hyperphagia, binge episodes, craving for foods with addictive attitudes, such as stealing food, are also common and are usually associated to increase of body weight, especially when there is a general reduction of activities. Th role of medications can be controversial. Sexual activity, when present, can be affected to, especially in the form of a reduction in all the sexually-oriented behaviors comparing to the baseline functioning.

3. Cognition and perception

PwID usually do not complaint about reduced ability to think and concentrate, but indirect signs can be indecisiveness and vacillation (Clarke et al., 1994). Depressive ID patients may appear dull, difficult to focus on tasks previously handled. The difficulties in engaging or finishing tasks may elicit irritability and unproportionate reactions. When indecisiveness and slowing are associated the person remains blocked, for example expanding the entity and duration of stereotypies or rituals. In severest cases the slowing of mental functions and the impairment of executive functioning are massive giving the impression of an abrupt regression involving the overall pragmatic functioning, not only cognitive skills, memory and logical-abstractive thinking.

Ideas of worthlessness, self-reproach, guilt, hopelessness and death are present in PwID beyond the intellectual deficit [(Benson and Laman, 1988, Charlot, 1997, Hurley, 2007, Pawlarcyzk and Beckwith, 1987). In verbal patients thought contents may be simple and very concrete. For example, a person with mild ID would often complain about the fact he/she cannot drive, work or going out with friends dancing. Thoughts of death are vague: in fact, the notion of death in typical children is usually developed at the end of childhood and further emotional development is required to fully conceptualize it. In most cases the ideas of death may regard the fear of losing persons or, when significant others are dead, the desire to reunite with them "in heaven". Hypochondriac preoccupations, usually associated to anxiety symptoms, are also frequent. Some individuals may verbalize punishment for themselves, for example "You have been bad, tomorrow you won't go in that place". In non-verbal patients these contents are for most virtually impossible to be assessed and very limited cognitive skills are supposed to impede the structuration of consistent holothymic ideation. On the other hand, it is possible that lower IQ patients experience during depression negative feelings about selves and others. Possible behavioral correlates could be, again, withdrawal but also seeking reassurance or physical contact of significant persons, beating themselves and crying. In more severe forms, these feelings may become pervasive, reaching a delusional intensity. The difficulties to correctly understand non-verbal communication, may influence the manifestations: PwID during depression may avoid food for the fear of harm; they may avoid or assault previously appreciated persons showing unmotivated hostility as they were afraid from them. PwID may experience the full range of psychotic symptoms, namely hallucinations. As in the general population, psychosis is less common during depression than mania. The behavior can be influenced by hallucinations and usually they are fully participated.

Bipolar Disorders

No data are available regarding the clinical features of BDII, cyclothymic disorder and BD NOS in PwID and LF-ASD nor about the differences in risk factors, course, prognosis and response to treatments comparing to BDI and other MDs, namely MDD. All the research has been focused on BDI and mania. To date, the studies regarding the clinical features of mania and BDI are at most limited to case reports, case series and chart reviews.

BDI in PwID may frequently assume the clinical and course features of BD in children, indicating the pathoplastic role of developmental level on the illness. Similar to the general population, BDI is associated to high familial load for BD but also other MDs and high rates of further comorbid PDs (Vanstraelen and Tyrer, 1999). Differences emerge instead regarding the course of the illness: in fact, comparing to the rates reported in neurotypical adults, highly unstable course characterized by rapid cycling (at least or more than four episodes per year) has been reported from 10% to 54% according to different sampling across the studies (Charlot et al., 1993, Glue, 1989, Goldberg and Harrow, 1999, King, 1999). In a review article about this topic, authors found that a greater severity of ID would be associated to shorter and more frequent episodes. In fact, they found that the mean number of episodes per year was around 25 per year in severe and profound ID comparing to 14.5 per year in BIF, mild and moderate ID (Vanstraelen and Tyrer, 1999). Comparing to rapid cycling in average IQ individuals, associated demographic and clinical features are not confirmed in PwID: thus, rapid cycling is associated to male rather than female gender (Cooper and Collacott, 1996, Vanstraelen and Tyrer, 1999). Moreover, rapid cycling in PwID is associated to young age at onset of the mood disorder and the rapid cycling, but also other psychopathology, often before the age of puberty (Vanstraelen and Tyrer, 1999). No medical illness has been specifically associated to rapid cycling, nor thyroid dysfunctions, instead very common among mid-age average IQ women with rapid cycling BD, neither epilepsy, which is associated to the severity of ID but not to the course of the bipolar illness (Vanstraelen and Tyrer, 1999). Interestingly, rapid cycling in ID are also associated to higher family burden for affective disorders, and this association is directly proportional to increased severity of ID. This evidence, together with the half of rapid cycling BD patients reporting the onset before 17 years of age, was explained by Vanstraelen and colleagues (Vanstraelen and Tyrer, 1999) as the effect of genetic anticipation in those patients with a familial load for BD. It is also possible that in those patients with a familial bipolar diathesis, constitutional emotional dysregulation may become prominent in the clinical picture and, on one hand it can facilitate or mediate the co-occurrence of BD in PwID and LF-ASD; on the other hand, emotional dysregulation may colour the manifestations of the affective disorder conferring to the episode and to the course an additional instability feature. If we consider these variables as independent, it is somehow possible that when the familial load and unspecified emotional dysregulation related to the neurodevelopmental basic condition co-exists, they have an additive effect producing these massively unstable affective pictures, alternatively called *ultra-rapid cycling*. Some questions, not yet answered, may arise considering the very high number of reported episodes and taking into account that, in our knowledge, no studies have considered the prevalence, features and relevance of mixed states in the ID population. In fact, it is possible that at least some of the cases diagnosed as ultra-rapid cycling BD might be actually better reframed as chronic mixed states, as some authors indicated in the past (e.g., (Reid and Naylor, 1976, Ruedrich, 1993). Probably, the emphasis given by DSM to the simultaneous co-occurrence of counterpolar affective symptoms, rather than the possibility of rapid shifts, alternation and co-existence in the same episode of both depressive and excitement symptoms, may have influenced the perspective and subsequently the poor interest toward this topic. It is suggestive that in samples of adolescents hospitalized for acute manic or mixed episode, the mean IQ is usually low, with about the 20% of patients having intellectual

disability. The 10% of the mixed manic episodes involve exactly patients with ID (Brunelle et al., 2009). Clinical pictures characterized by a combination of withdrawn, underactive behaviors alternating with agitated, restless behaviors, extreme reactivity and dysphoria in response to demands have been described (Charlot, 1997). It is quite hard to define such mixed states according to current DSM-5 specifiers as depressive or manic episodes with mixed features.

Comparing to the peers with ID and other PDs, bipolar ID patients reported higher rates of thought disturbances, even when compared to primary psychotic disorders, including misinterpretations and obsessive thinking, severer functional impairment and higher rates of PBs, mostly aggression, self-injury and disruptive behaviors (Fletcher et al., 2016). Interestingly, DSM symptoms of mania, taken individually, are not specific for the diagnosis of mania but are commonly associated to other psychopathology with the exception of the decreased need for sleep. The most reliable parameter is the variation of the symptoms along a significant time frame (Gonzalez and Matson, 2006).

Noteworthy, some authors claimed the prominence of non-mood symptoms in ID, especially for mania (Cain et al., 2003). This can be a particularly relevant issue in the case of LF-ASD, in which background irritability and mood dysregulation may be core features of the neurodevelopmental disorder. Unfortunately, this aspect is critical to the under-meeting of current categorical criteria for BD. Anyway, manic symptoms may be decomposed according to the three main dimensions of functioning relying to affective disorders.

1. Mood

Mania in PwID and LF-ASD may be characterized by both euphoria and irritability, but dysphoria, over-reactivity and extreme lability are usually prominent (Fletcher et al., 2016). DM-ID-2 does not provide adaptation for manic mood, but examples are given in the note for hypomanic mood. Elated mood may rapidly alternate with irritable mood, both spontaneously or reactively to environmental stimuli. The reaction is usually disproportionate to the type and intensity of the stimulus. Temper tantrums are also common during excitement. Patients may appear cranky, extremely happy or cheerful without any reason, silly, excessively giddy, loud and they can inappropriately laugh or sing, they can be intrusive and excessively pushy with others. Even the mimic and gestures are usually coherent and expressive of the current affective state: for example, patients may appear excessively or inappropriately smiling, sometimes fatuous and poorly in agreement with the environmental emotional atmosphere.

2. Activity and behavior

Psychomotricity is usually increased during mania. This acceleration may cover a range of manifestations including increased energy and movements, fidgeting or restlessness, up to agitation in severest cases. Sometimes stereotypies, when present, may result augmented. The speech may be accelerated and pressured. When the acceleration is accompanied to a formal disturbance of the thought, the speech can become less understandable and eventual pre-existing motor language disorders may be accentuated. In non-verbal patients it can manifests as increase in volume and tonality of vocalizing and loudness. It is possible to evidence the intensification of the engagement in daily activities or the person may become overdemanding toward others to make more activities. For example, a person may ask to leave home and go out walking more than usual,

and may become cranky or aggressive when it is not possible to be satisfied. The research for interpersonal interactions is often elevated: the person may show jocularity but intrusiveness, scarce respect of social rules and impulsivity may make the social behavior problematic and inappropriate. During mania the acceleration can be so high that the behavior may become actually disorganized, characterized by actual purposeless hyperactivity, running or wandering away: thus, the person can show an abrupt regression of previously handled adaptive skills.

Increased sexual impulse and activity is an important sign of excitement, in some cases becoming prominent and qualifying oligo- or mono-symptomatic manic forms. Hypersexuality usually consists in a large increase of masturbation (Pary et al., 1999). This activity may be poorly controlled and the patient does not take care of the surrounding environment. Poor social skills and pre-existing disinhibition may be further affected during (hypo)manic phases and sexually-oriented behaviors may be not only increased but also socially challenging: unrequested or socially inappropriate research of physical contact is very frequent, and can range from insistent attempts to touch others, in some cases with poor distinction of gender preference previously expressed, up to get undress in public circumstances, exhibition of genitals and, in severest cases, a strict surveillance is required to avoid sexual assaults.

Among the neurovegetative signs, reduced need for sleep is an early sign of excitement, which unfortunately may be masked or under-recognized in patients taking sedative medications. Even appetite can result affected, usually increased and associated to voracity, sometimes binge eating with pushy and continuous requests of food. It is not uncommon that patients steal food from others during the meal as well as along all the day, especially during night. In some cases, manic ID patients may become actually seeking for food or beverages and may show a sort of craving toward them.

PBs are very commonly associated to excitement in PwID and they may be underlain by different motivations according to the degree of ID. In BIF and mild ID, oppositional defiant behaviors, threating and aggressiveness, are commonly elicited by the need to obtain secondary advantages such as full attention, objects or the satisfaction of other requests. In fact, during hypomania and mania, the sensitivity to frustration, reject and the capacity of respecting timing and delay the reward may result increased comparing to the baseline or fully compromised. Throwing away or breaking others people's objects, dirt things, losing control of urines and feces on purpose, manipulating or eating them, are non-aggressive defiant behaviors commonly found in severer degree of ID. Self-injury may also be present, but recent data suggested that is less specific for mania comparing to aggressiveness toward others or objects (Baudewijns et al., 2018).

3. Cognition and perception

Cognition and perceptual disorders are difficult to be evaluated in PwID and their assessment is challenging for most patients. Flight of ideas or accelerated thoughts may be more easily evinced by acceleration of the speech and a tendency to pass from a conversational topic to another without any kind of reciprocity or respect of the rules of the conversation. However, it is common especially when ASD coexists, that the person with ID shows focused and restricted interests with a tendency to perseverance and difficulties in following the course of the conversation. Thus, a significant qualitative difference in the speed of thoughts and speech has

to be detected comparing to the usual. Distractibility is a common feature of (hypo)mania in PwID and LF-ASD as well as in neurotypically developed patients. However, baseline cognitive deficits may include alterations in executive functioning such as the attention flexibility, shift and maintenance, planning and control of the task, cognitive impulsiveness. These deficits may imply short-living time for the execution in tasks and the need for support of care-givers to remain engaged in a task. Pleasant tasks or activities of special interest for the person may not be affected. To identify distractibility as a feature of (hypo)mania in PwID, the clinician should formulate target questions focused on those tasks in which the person can remain usually well engaged. Increased distractibility may also be evinced when external low stimuli (noises, others talking, etc.) capture the attention of the patient differently than usual, interfering with activities normally performed. The performance has to be significantly impacted by such a distractibility and it may seem that the PwID lost some skills, for example the capacity to remember and perform well-known sequences of actions.

Disturbances of the thought content is not uncommon during mania. Increase of the self-esteem is difficult to evaluate as strange beliefs or scarce self-awareness of the own limitations may be present as features of the basic condition and in agreement with a low developmental level. By the contrary, grandiosity may regard simpler contents than average IQ patients. For example, a PwID may develop the belief he/she can drive the car boasting about having driving license, he/she has a romantic relationship with a neighbor, he/she is an educator etc. This content is not actually evaluable in persons with severe and profound ID and with severe communication impairment. It is possible that risky behaviors (for examples fugues or try to "fly") are dragged by megalomaniac beliefs rather than impulsiveness or defiance, but it can be very hard to settle the actual motivation of such behaviors, especially because one reason does not exclude the others. Sudden avoidance of places, persons, activities or objects, food for example, may suggest delusional beliefs even if these symptoms follow in differential diagnosis with anxiety and panic attacks in persons with moderate-to-profound ID.

PwID present the full range of perceptual disturbances, but the differential diagnosis with normal behaviors can be challenging especially in LF-ASD. In fact, autistic persons may often present self-talk. It mostly represents a reiterative self-dialogue in which they repeat, often with pronominal inversion, sentences, orders or suggestions heard in the previous day. Sometimes the autistic self-talk is stereotypic in nature. The presence of auditory hallucinations may be suggested when the person suddenly interrupt the ongoing activity and may appear frightened or withdrawn from the social context. Similarly, the person with poor or without verbal skills, may appear freezing, or looking at places in the room where there is nothing to see or may behave as something terrific was there or on the body. Beating, scratching or hiding parts of the body, wearing peculiar dresses may all be behavior related to visual or tactile misperceptions.

These symptoms have to be carefully investigated because hallucinations, especially visual ones, disorganization and alarm state may be also arisen during delirium which requires a different management.

As illustrated in the above descriptions of manic features in persons with ID and LF-ASD, *behavioral equivalents* may have the value of additional validators of the diagnosis. This concept is clearly exemplified in a significant study conducted by the group of Matson (Sturmey et al., 2010): the authors explored the

symptomatic factors associated to the diagnosis of mania in PwID. They found four main factors accounting for around the 40% of the variance. The first factor of mania, accounting for the 20% of the variance, was characterized by verbal maladaptive behaviors toward others and impulsiveness, for example curses and imprecations, verbal abuses and repetitiveness about some subjects or concerning over and over. These behaviors also cluster with easy frustration, loudness and accelerated speech and, at lesser extent, with irritable mood. The second factor, including distractibility, was characterized by attention-seeking, demanding and defiant behaviors (for example throwing objects, hitting, kicking or pinching people). The third factor included euphoric mood, restlessness and agitation and talking quickly. Interestingly, increased stereotypies such as rocking, flapping, spinning and amusing with repetitive behaviors belong to this factor. Finally, the fourth factor included equivalents of psychomotor activation and decreased need for sleep: related behaviors are temper tantrums, opposition to instruction or guidance, aggressiveness and screaming.

1.7 ASSESSING INSTRUMENTS

Standardized assessing instruments represent a valuable resource for the psychopathological diagnostic process in PwID and LF-ASD. Indeed, they complement, fasten and optimized more than in the general population the collection of clinical information usually performed by means of the interview and direct observation of behaviors. Moreover, they favour different professionals to share clinical judgments and projects.

The psychopathological evaluation of neurodevelopmental disorders has been substantially expanded only in the last three decades. Specialized researchers of this field worked on one hand on the development of *ex novo* tools, on the other hand on the translation and adaptation of tools previously developed for the general population. In both the cases, the assessing instruments show several applicability and efficacy limitations. Adapted questionnaires also show limited sensitivity, mainly due to the significant atypicality of psychopathological symptoms in PwID and LF-ASD.

Currently, the most popular assessing tools are general screenings, aimed to give indications toward all the diagnostic categories compatible with occurring symptoms and behavioral equivalents, rather, psychopathological area-specific instruments also exist. Otherwise, there are few standardized diagnostic interviews: they are usually long, expensive and less useful for the multidisciplinary collaboration. By no means, the systematic application of standardized assessing tools to support and integrate the diagnostic process, the monitor of course and treatment outcomes is fundamental in the ID and LF-ASD population. Advantages are summarized in **Table 1**.

Table 1. Advantages for the use of standardized tools in the diagnosis and management of psychopathological issues in persons with ID and LF-ASD

To support in the diagnostic process, especially regarding behavioral equivalents in persons with sever-to-profound ID
To favour the direct involvement of the persons with ID/ASD and caregivers in the assessment pathway
To facilitate the comparison and discussion among professionals and different context
To increase interdisciplinary sensitivity and specificity toward behavioral equivalents
To enhance the multidisciplinary cooperation
To draw objective evaluation of the intervention's results
Continuous improvement of standardized instruments
To improve the evidence-based research
To expand the knowledge about the peculiar and specific presentations of psychopathological symptoms and syndromes.

1.7.1 STANDARDIZED DIAGNOSTIC INTERVIEWS

The few standardized diagnostic interviews for the investigation of psychopathology in PwID and LF-ASD are mainly addressed to persons with good communicative and introspective abilities (Heal and Sigelman, 1995).

The most famous is the Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD), developed by Stephen Moss e co- for the evaluation of PDs in adults with ID workers (Moss, 2011, Moss et al., 1994, Moss et al., 1993); it is based on ICD-10 categories and criteria. In fact, it is derived from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), semi-structured clinical interviews made by the World Health Organization in 1994, starting from the Present State Examination (PSE) (Wing et al., 1974), and used by specifically trained clinicians to support the diagnosis of PDs in adults. Recently, correspondence profiles with DSM diagnoses have been proposed.

PAS-ADD includes 145 questions originally referring to seven subscales corresponding to the main Axis I PDs, thus excluding personality disorders: schizophrenia and other psychotic disorders, bipolar disorder, depression, anxiety disorders and phobias, obsessive-compulsive disorder, autistic spectrum disorder and hyperkinetic disorders (including ADHD). The clinical interview is not able to detect all the disorders codified in the diagnostic manuals, but only those ones diagnosable by means of an interview. Direct questions about ASD and ADHD are not included, nonetheless it is possible to make their diagnoses due to specific sections in integrative instruments.

PAS-ADD is a semi-structured interview designed to be used by physicians. It is available in two versions: the first for those cases which allow the direct interview of the PwID, the other dedicated to the interview of a *proxy*, a person who knows very well the patient. In both cases the diagnosis is formulated using the adaptation of SCAN informatized algorithms. The authors compared the scores obtained with the two versions of the instrument and found low convergence (41%). Thus, they suggested to always administer both the versions to improve the diagnostic sensitivity. The psychometric properties of PAS-ADD have been evaluated by Costello, Moss, Prosser e Hatton (Costello et al., 1997, Moss et al., 1997). The inter-rater reliability of the direct version has been measured by means of a session in which some clinicians autonomously completed several questionnaires basing on the view of registered interviews. The reliability was low for both the individual items and diagnostic groups (Cohen's K = .65 e .66, respectively). A factorial analysis identified for each subscale a factor with a good reliability with the clinical diagnoses: the PAS-ADD diagnosis agreed with the pre-existing psychiatric diagnosis in the 76% of the probands. No information was given about internal consistency and test-retest reliability. The results of other researchers and the experience of several clinicians indicated that PAS-ADD would seem useful for the screening of mental health issues rather than to identify a specific PD. Comparing to the Mini e Checklist versions, the PAS-ADD would be preferred when the evaluation is addressed to an intellectually disabled person with good verbal skills, the aim of the evaluation is to draw a ICD-10 or DSM-IV-TR diagnosis for administrative purposes and/or there is the suspect for psychotic disorder, as this tool is particularly sensitive in this domain. Around a decade ago, the PAS-ADD has been

adapted also to children and adolescents, the Child and Adolescent Psychiatric Assessment Schedule (ChA-PAS) (Moss et al., 2013).

The Psychopathology Checklists for Adults with Intellectual Disability (P-AID) (Hove and Havik, 2008) is a more recent interview. It is a set of tools to be used with informants, and is aimed to identify 10 PDs and 8 PBs according to DC-LD (Psychiatrists, 2001). The P-AID sowed good internal consistency and inter-rater reliability, 8 orthogonal dimensions in the factorial analysis, whereas sensitivity and specificity are still to be evaluated (Hove and Havik, 2008). P-AID is convenient comparing to PAS-ADD because it includes a detailed evaluation of the main PBs; otherwise it is not directly usable with the person with ID or LF-ASD and this a disadvantage.

Another semi-structured interview is the Schedule for the Assessment of Psychiatric Problems Associated with Autism (and Other Developmental Disorders) (SAPPA) (Bolton and Rutter, 1994). This interview too has been developed in United Kingdom and it includes items derived from the Research Diagnostic Criteria developed by Spitzer, Endicott e Robins (Spitzer et al., 1978). It has to be directly performed with the evaluated person or, in case of severe communication impairment, to a family member or other significant persons. Its main purpose is to help clinicians in identifying in ASD persons significant variations of behavioral features which may represent symptoms of one or more co-occurring PDs. Once detected, the symptoms are defined on the chronological and nosographic levels. This instrument defines a behavioral change as relevant when it is clearly out of the range of usual behavioral variations of that specific person, it is associated to psychotic symptoms (delusions, hallucinations, catatonia, etc.) or it markedly impairs the functioning, as indicated by the appearance of alterations in at least one of the main life areas: interests, self-care, social involvement, drive, supervision, housing arrangement, and work (Bolton and Rutter, 1994). The clinical relevance of a behavioral change is further investigated according to whether or not it can be managed by oneself or a care-giver intervention is required. The duration of symptoms has to be defined accounting for the context in which they appeared and maintained, eventual extraordinary life events or circumstances, such as loss, bereavement, therapy changes, or health issues. Episodic PDs identified by SAPPA are mood, anxiety and psychotic disorders. The interview includes questions about the familial psychopathological history and related to PBs and other issues without episodic course. The tool has been used in some epidemiological studies (Bolton et al., 2011, Bradley and Bolton, 2006, Hutton et al., 2008, Raznahan et al., 2006), mainly with for research purposes and with ASD persons (without apparent co-occurring ID), often needing modifications to be fully applied. An attempt to adapt it to clinical use has been recently made (Battaglia et al., 2016), whereas a validation study and the evaluation of its psychometric properties have never been performed yet.

The last standardized diagnostic interview to note is one specific for anxiety and mood disorders, the Mood and Anxiety Semi-Structured Interview (MASS) (Charlot et al., 2007a). It has been designed to be used with usual caregivers of persons with ID and LF-ASD and it is made of 35 items, corresponding to likewise DSM symptoms or behavioral equivalents. The time frame covered is the month preceding the evaluation. The MASS showed good sensitivity and specificity, with high rates of concordance with clinical diagnoses and Hamilton Depression Rating Scale scores (HDRS) (Hamilton, 1967).

It has to be noted that none of the above-mentioned assessing tools have an Italian validated version.

1.7.2 SCREENING TOOLS

The first published psychopathological screening for PwID is the Psychopathology Instrument for Mentally Retarded Adults (PIMRA) (Matson et al., 2012, Matson et al., 1984, Senatore et al., 1985), which has been demonstrated to be efficacious in the research, planning and evaluation of intervention outcomes. The interview, available for self and hetero-administration, is composed by 8 subscales, each including 7 dichotomous items (Yes/No). The item content is strictly related to the main symptoms of the major diagnostic categories (schizophrenia, depression, psychosexual disorders, adjustment disorders, anxiety, somatoform and personality disorders), as they were described in the DSM-III ((APA), 1980). A subscale evaluates the absence of psychopathological issues. The individual scoring is possible by means of a comparison with the reference sample in the form of percentage. The firs study by Matson and colleagues (Matson et al., 1984) confirmed high levels of internal consistency as well as acceptable test-retest reliability. However, other studies (Linaker, 1991, Minner et al., 1994, Sturmey and Ley, 1990) indicated low inter-rater reliability. The psychometric properties of PIMRA were examined by its developers. The internal consistency was .85 e .83 respectively for the direct and the informant versions. The split-half reliability showed high scores (.88), even if lower for the proxy version (.65). The test-retest reliability of the patient version was acceptable for the total scale (.68), while was from low to acceptable for each of the 8 subscales (da .42 a .68). The test-retest reliability of the informant version was higher for the total scale (.91) comparing to the area-specific subscales (from .48 to 1.00). The correlation between the scores of the subscales and the total scores was low for both the versions (from .01 a .30 for the subscales and .18 for the total scale). The validity of the instrument has been investigated basing on the concordance with the Affective Disorder (Depression) subscale of the informant version of the Beck Depression Inventory (BDI) (Beck and Steer, 1987) and the Zung Self-Rating Depression Scale (SDS) (Zung, 1965). The concordance was very high. The construct validity has been examined for the Schizophrenic Disorder subscale (Linaker and Helle, 1994, Swiezy et al., 1995), and the Psychosexual Disorder subscale (Matson and Russell, 1994), whereas a rigorous evaluation of the remaining 5 subscales is lacking. The factorial analysis of PIMRA (Balboni et al., 2000, Sturmey and Ley, 1990) produced poorly clear and reliable results. The authors identified four main factors and suggested that the 8 subscales are not referred to independent constructs. The inter-rater reliability is discordant across the studies (Linaker, 1991, Minner et al., 1994, Sturmey and Ley, 1990). It seemed that PIMRA may produce false negatives among those persons with more severe ID because of the missing compilation of those items implying high language and abstractive thinking skills (La Malfa et al., 1997). Reproducibility of the results among different evaluators have been attributed to different professionals or in absence of a specific training (Havercamp and Reiss, 1996).

The second instrument, considered a sort of evolution of PIMRA, is the *Diagnostic Assessment for the Severely Handicapped* (**DASH**) (Matson et al., 1991), developed in 1991 and revised in 1995 (**DASH-II**) (Matson, 1995). It is a questionnaire evaluating the presence of PDs in persons with severe and profound ID. It includes 84 items organized in the following subscales base on the DSM-III-R diagnostic criteria ((APA), 1987):

Anxiety, Depression, Mania, Pervasive Developmental Disorder/Autism, Schizophrenia, Stereotypies/Tic, Self-injurious Behavior, Elimination Disorders, Eating Disorders, Sleep Disorders, Sexual Disorders, organic Syndromes, Problems with Impulse Control and Behavioral disturbances. DASH evaluates frequency, duration and severity of each symptom and is administered to an informant with a good knowledge of the PwID. The psychometric characteristics have been evaluated in some studies. Sevin, Matson, Williams e Kirkpatrick-Sanchez (Sevin et al., 1995) found the validity and test-retest reliability to be .84 for frequency, .84 for duration and .91 for severity. The internal consistency was from poor to moderate for different subscales with Cronbach's alfa ranging from 53 and .84 (Paclawskyj et al., 1997). The factorial analysis showed not univocal results. Matson, Coe, Gardner e Sovner (Matson et al., 1991) evidenced 6 factors: emotional lability, aggressiveness/conduct disorders, language disturbances, social withdrawal/stereotypies, eating and sleep disorders. Afterwards, Sturmey, Matson e Lott (Sturmey et al., 2004) identified a similar structure but only 5 factors emerged: emotional lability, language disturbances, sleep disorder psychosis and anxiety. The concurring validity has been tested comparing DASH-II with the Aberrant Behavior Checklist (ABC) (Paclawskyj et al., 1997). The investigation showed that the subscales Mania, Organic Syndromes and Impulse Control and Behavioral Disturbances were highly related with the Irritability and Hyperactivity ABC subscales. The subscales Pervasive Developmental Disorder/Autism and Stereotypies/Tic were correlated with the ABC subscale for stereotypic behavior (Paclawskyj et al., 1997). Further evidence confirmed the validity of Mania and PDD/Autism subscales (Matson and Smiroldo, 1997, Matson et al., 1998) Similarly, the depression subscale of the DASH-II underwent a validation procedure by comparison with the DSM-IV diagnosis. By excluding too peculiar presentations, the DASH-II depression scale resulted to identify around the 93% of clinically depressed subjects (Matson et al., 1999). Moreover, the authors found that the depressive clinical picture in sever and profound ID would be predominantly characterized by symptoms non-verbal in nature pertaining to sleep and eating difficulties, psychomotor disturbances, and irritability frequently associated to abnormal behavior such as aggressiveness, stereotypies, noncompliance, unresponsiveness to the environment, and manic symptoms.

One of the numerous studies from the group of Matson (Matson et al., 1997) also evidenced that in persons with severe and profound ID anxiety symptoms would be evaluable only via their behavioral correlates, with the subsequent risk of insufficient diagnostic sensitivity and need for the development of more refined tools. The data of the literature indicate that the DASH-II is the most used assessing instrument in clinical and epidemiological studies, including those addressing the psychiatric morbidity in persons with severe and profound ID at the opposite poles of the life, adolescence or young adulthood (Bradley et al., 2004) as well as among the elderly (Cherry et al., 1997). The general reliability has been confirmed over and over again. However, further research is needed to demonstrate the construct validity of all the subscales. DASH-II has been adapted in Italian by Guaraldi, Ruggerini, Neviani e Vicini in 2002.

The Mini version of Psychiatric Assessment Schedule for Adults with Developmental Disabilities (Mini PAS-ADD) (Prosser et al., 1998) and the Checklist (PAS-ADD Checklist) (Moss et al., 1998) are currently the main assessing instrument used in Europe in clinical studies involving PwID. Both the versions are based on the

PAS-ADD Interview. The Mini PAS-ADD was developed in 1998 by Prosser and colleagues with the aim to evaluate mental health issues in PwID with every severity level. It is a semi-structured interview administered to a caregiver. It can be used even by someone without clinical competencies after a brief training. Mini PAS-ADD includes a questionnaire with 64 items corresponding to likewise symptoms. A severity score is attributed to each item and significant life events are listed in a dedicated checklist. Clinical items are grouped in 7 subscales related to the major Axis I PDs: Depression, Anxiety, Bipolar Disorder, Obsessive-Compulsive Disorder, Psychosis, Not Specified Disorder (including Dementia), Autism Spectrum Disorder. It is possible to calculate the single subscale score. The over-the-threshold scores indicate the possible co-occurrence of a disorder and suggest the need for a direct detailed clinical evaluation. The evaluation of the psychometric properties (Moss et al., 1998) evidenced a moderate internal consistency (Cronbach's alfa ≥.8) for four subscales and lower for the others (Cronbach's alfa ranging from .6 e .8). The inter-rater reliability, including psychiatrists and community operators, was low for the overall subscales (Spearman's r ranging from .32 e .65). The construct validity was examined comparing the Mini PAS-ADD with subsequent psychiatric diagnoses. With regards to the presence or absence of a PD the concordance was of 91%, but the results of each subscale were not consistent. Afterwards, the Mini PAS-ADD has been indicated by other researchers as useful as a screening rather than a diagnostic instrument. Nonetheless, the Mini PAS-ADD has been used by several epidemiologic studies with great scientific value, pertaining both ID and ASD. The manual provides a clinical glossary which can be used to collect information about symptoms directly by the informant, a description of the formation pathway and coding exercises.

Other significant tools that deserve a mention are the Developmental Behavior Checklist for Adults (DBC-A) (Einfeld and Tonge, 1995) aimed to measure a wide range of emotional and behavioral problems in adults with ID, the Assessment of Dual Diagnosis (ADD) (Matson and Bamburg, 1998) developed to detect the full range of PDs in adults with mild and moderate ID and the Reiss Screen for Maladaptive Behavior (RSMB) (Havercamp and Reiss, 1996), a general screening completed by care-givers.

1.7.3 ASSESSING TOOLS DEVELOPED IN OUR COUNTRY

The first Italian tool specifically addressed to PwID was the "Valutazione degli Aspetti Psicopatologici nell'Handicap" the eValuation of Psychopathological Aspects in Handicap (VAP-H) (Pilone et al., 2000), developed on the basis of the ICD-10 diagnostic criteria ((WHO), 1999). The items are presented in sparse order to reduce influencing phenomena by the completer. Several items belong to more than one category as they refer to symptoms possibly present to different syndromic pictures. A first validation of the tool has been conducted according to the empirical method by the comparison of VAP-H diagnoses and those traditionally formulated with ICD-10 in a large sample of PwID. A further control confirmed the precision and validity of the instrument. The purpose of VAP-H is to collect structured and objective information about behavioral and socio-emotional aspects, as well as to facilitate and orient the psychopathological diagnosis.

Its use allows the identification of the main psychopathological traits, to note their frequency, and to obtain indications related to ICD-10. At most, VAP-H represents a semi-structured support to the clinical diagnostic

procedure and their results are not summarized in a score. It allows longitudinal comparisons useful to monitor the psychopathological course and the effectiveness of therapeutic interventions. Some limitations have been argued regarding the procedure used for the item's construction. The items were derived by the conversion of symptoms described in ICD-10 which, although is one of the most famous and used international classification systems for mental health issues, it remains a valid model only in Europe. Another problem pertains the excessive length of the VAP-H, which may imply quality data variations or errors.

In the last ten years the research group of Marco Bertelli in Florence worked on the development of a complex panel of assessing tools aimed to implement the diagnostic evaluation and subsequent follow-up of PDs in PwID and ASD, with a specific attention to those persons with marked communication and conceptualization difficulties, the Systematic Psychopathological Assessment for persons with Intellectual and Developmental Disabilities (SPAIDD). The SPAIDD system was designed in order to overcome some of the issues detected for other similar tools, such as inapplicability to all the levels of ID, lacking alignment to DSM (DSM-5 specifically), the tendency to overlook some symptoms or main syndromes, the paucity of differential chronological criteria, long time required for the administration, and poor interdisciplinary availability. Some of these tools showed weaknesses in the commonest psychometric properties, such as test-retest reliability and inter-rater reliability (Bertelli, 2019).

The SPAIDD panel include tools for each phase of the clinical intervention, such as the psychopathological screening, the specific categorical diagnosis, the dimensional diagnosis and the following symptomatic follow-up. The items of every tool belong to a unique set of behavioral equivalents and psychopathological symptoms related to the major PDs. The tools are mostly base on observable behaviors and can be administered to persons who know very well the person with ID. This aspect allows to overcome the limitations related to severe cognitive and communication impairments. However, the manual provides for each equivalent full description encompassing examples from clinical practice related to a large span of abilities or reported phrases also regarding feelings and thought contents. In this perspective, the intellectually disabled person able to answer may participate to the own evaluation integrating information. Thus, all instruments can be indiscriminately used regardless the ID level and the presence of ASD, are aligned with DSM-5 ((APA), 2013)be, require brief or very brief time for the training, are usable from multiple professionals. The area-specific instruments also evaluate the chronological presentation of symptoms, supporting clinicians in drawing differential diagnosis and prognosis.

The General version (**SPAIDD-G**) is the first SPAIDD instrument according to both its order of development and utilization. It is a screening tools and support professionals participating to clinical and rehabilitative activities in evaluating the presence and type of a psychopathological condition, rather to determine the level of symptomatic equivalence of one or more significant behavioral variations. SPAIDD-G evaluates the following syndromic groups, according to DSM-5: eating/feeding disorders, psychotic disorders, mood disorders – depression and mania separately, anxiety disorders, medications' side effects, delirium, dementia, substance-related disorders, odd, dramatic and anxious personality disorders separately, impulse control disorders, autism spectrum disorder, identity dissociation disorders, somatic symptom disorders, sexual

disorders, obsessive-compulsive disorders. SPAIDD-G has been perfected along time up to the current version, SPAIDD-G 1.9 (Bertelli, 2019), updated to DSM-5. In this version further improvements toward a higher diagnostic specificity have been carried by the addition of criteria for relative syndromic weight, syndromic specificity, and clinical relevance of the scores. SPAIDD-G passed through various validation processes (Bertelli et al., 2012). The concordance was evaluated in subsamples with DASH-II and diagnoses formulated by expert clinicians according to DSM criteria and validation samples included PwID from mild to profound. The psychometric properties of the SPAIDD-G 1.9 (Bertelli, 2019) resulted overall good. The correlation analyses among syndromic groups were variable but consistent for the majority of psychopathological orientations (Spearman's r ranging from .02 and .95), and the correlations between the total scores and each orientation showed similar results (Spearman's r ranging from .30 and .97). The internal coherence of overall scale resulted adequate (Kuder-Richardson's coefficient - KR20 .84) whereas the internal coherences of each syndromic group are variable, ranging from .14 and .81. The Cohen's k for inter-rater reliability was equal or superior of .76. The face and criterion validity were on the whole was good. The study of concurrent validity was limited by the paucity of comparable validated assessing instruments translated in Italian. Generally, the comparison with DASH-II showed SPAIDD-G to have similar or higher face validity, applicability and syndromic sensitivity. The time required for the administration was generally lower.

1.7.4 ASSESSING INSTRUMENTS FOR THE EVALUATION OF MOOD DISORDERS

Most area-specific instruments consist in adaptations of tools originally developed for the population with typical neurodevelopment. Such instruments have been extensively demonstrated useful when applied to persons with good cognitive and communication skills but their sensitivity and reliability are much lower in case of more severe impairment.

Several instruments have been developed to detect MDs, probably because their marked importance in clinical practice with PwID. Among the main instruments are: Affective Rating Scale (Wieseler et al., 1988); Hamilton Depression Scale – Mental Handicap Version (HDSMH) (Sireling, 1986); Beck Depression Inventory (BDI) (Kazdin et al., 1983); Mental Retardation Depression Scale (Meins, 1993, Meins, 1996); Self-Report Depression Questionnaire (SRDQ) (Reynolds and Baker, 1988); Zung Depression Inventory – Mental Handicap Version (ZDI-MH) (Deb et al., 2001b, Helsel and Matson, 1988); Intellectual Disability Mood Scale (IDMS; Argus, Terry, Bramston e Dinsdale, 2004); Anxiety, Depression, and Mood Scale (ADAMS) (Esbensen et al., 2003); Mood, Interest & Pleasure Questionnaire (MIPQ) (Ross and Oliver, 2003); Glasgow Depression Scale for people with a Learning Disability (GDS-LD) (Cuthill et al., 2003). Noteworthy, none of them have an Italian translation. The Hamilton Depression Scale – Mental Handicap Version (HDS-MH), the Beck Depression Inventory (BDI) and the Zung Depression Inventory – Mental Handicap Version (ZDI-MH) are adaptations of the corresponding assessing instruments for the general population.

The psychometric properties of the Self-Report Depression Questionnaire (SRDQ) have been tested by Esbensen, Seltzer, Greenberg e Benson (Esbensen et al., 2005), comparing the data of pre-existing studies. The validity and reliability resulted good, sometimes actually excellent.

The Intellectual Disability Mood Scale (IDMS) also showed good psychometric properties, although it has been tested almost exclusively in persons with mild ID. It is characterized by six dimensions: rage, confusion, depression, tiredness, tension and energy. These dimensions are evaluated through a 5-point Likert scale, presented to the evaluated persons as buckets filled with increasing levels of liquid. Thus, good abstractive and logical skills are required to complete it.

The Anxiety, Depression, and Mood Scale (ADAMS) is usable with any ID level. It is constituted by 28 items to be scored on the basis of information obtained by someone who knows the person very well. Items are organized in 5 subscales: Manic/Hyperactive Behavior, Depressed Mood, Social Avoidance, General Anxiety, and Compulsive Behavior. The internal coherence of each subscale resulted satisfactory (Cronbach's alpha ranging from .75 and .83), as well as test-retest reliability (correlational coefficients ranging from .72 to .83).

The Mood, Interest & Pleasure Questionnaire (MIPQ) includes 25 items with a Likert-scale scoring, it is organized in two subscales for Mood and Interest and Pleasure; it can be used with persons with severe ID and LF-ASD. MIPQ has shown excellent internal coherence (.94) and good reliability. Both test-retest and inter-rater, respectively .87 e .76. The concurrent validity has been demonstrated through the comparison with the Aberrant Behavior Checklist (ABC), mostly with the ABC subscales Lethargy and Social Withdrawal, interpreted as indices of good construct validity.

A particularly promising tool is the Glasgow Depression Scale for people with a Learning Disability (GDS-LD), whose peculiarity is the integration of information collected by both the PwID evaluated (mild to moderate ID) and caregivers and proxies. At this purpose the tool is divided in two parts comprehending 20 and 16 items, respectively. The evaluation of the psychometric properties gave promising results.

Noteworthy, none of the above cited assessing tools specifically developed for PwID refers to the categorical classification systems, ICD and DSM. There are many advantages in this approach, which is at most dimensional, mainly aimed to a clinical utility and, in the research perspective, addressing the issue of peculiar clinical presentations of MDs in ID. Moreover, few of them account for mania and its softer forms. Otherwise, the reference to a major classificatory system appears crucial in some ways. To correct frame patients according to commonly shared, univocal diagnostic categories has significant implications: improvement of the psychiatric diagnosis and administrative coherence with clinical needs, development and correct application of treatment guidelines with subsequent reduction of health care inequalities, expansion and improvement of research standards in this field. An optimal instrument should account for this aspect without losing the sensitivity and specificity toward the peculiarities of PDs in ID and LF-ASD.

CHAPTER 2

MATERIALS AND METHODS

2.1 Study design

The present study has been designed as an observational, prospective, cross-sectional, multicentric, single arm study.

The main objective of the study was the validation of the version for MDs (depressive and bipolar disorders) of the Systematic Psychopathological Assessment for persons with Intellectual and Developmental Disabilities (SPAIDD-M). A secondary aim was the identification of the prevalence and clinical features of MDs in subjects with ID and LF-ASD. Primary outcomes were represented by measures of SPAIDD-M psychometric properties, including: content, face, construct and criterion validity, reliability, internal consistency (sensitivity and specificity), and test-retest reliability. Secondary outcomes consisted of prevalence rates of DDs and BDs in people with ID and LF-ASD as well as demographic, anamnestic, familial and clinical data associated with this comorbidity. Clinical data included course and other specificities of MDs in this population as well as response to psychopharmacological treatments.

2.2 Participants, procedure and setting

The study sample was composed of 233 adults, including 64 women and 169 men. Socio-demographic characteristics of the sample are shown in **Table 2** (chapter 3).

The study included individuals aged 16 years and older with a diagnosis of ID or LF-ASD according to the DSM-5 criteria ((APA), 2013). There were no exclusion criteria with the exception of the cut-off for age. The presence of co-occurring relevant genetic and medical issues was registered but was not considered a limitation for the participation to the study according to its naturalistic, non-interventional design.

Study participants have been randomly or consecutively recruited among those attending the psychiatric services of the Research and Clinical Centre (CREA) of the San Sebastiano Foundation of the Misericordia di Firenze. The broad network of CREA throughout Italy was involved in the data collection. In fact, the present study is an appendix of a study protocol approved by the Ethical Committee of the University of Florence (number of the study protocol: CEAVC 14828), the "Autism and Psychopathology: Prevalence, Identification, and Symptoms Equivalence" study (APPrISE), made in collaboration with the Italian Society for Neurodevelopmental Disorders (SIDiN) and the Italian Foundation for Autism (FIA). APPrISE is aimed to evaluate the prevalence of psychiatric disorders in people with ASD and/or ID via the administration of SPAIDD-G and other psychopathological assessing instruments. At the time of the realization of the present study, the APPrISE network included around 60 participating centres across Italy. Clinicians and researchers recruited as evaluators are psychologists and psychiatrists: they received an initial training on the use of the assessing tools. The CREA team was available to give full and continuous support by mail and phone in case of doubts or difficulties. Some of the external evaluators (pertaining to 12 centres) of the APPrISE study accepted to include in the assessing sessions of some probands the administration of SPAIDD-M. They were

trained and supported also for this part of the study. This procedure may be considered a source of referral bias that will be discussed later.

Thus, the inclusion of different centres provided the expansion of recruitment settings: outpatient services specifically addressed for ID and ASD persons, including psychiatric ambulatory for ID/ASD adults, residential facilities (from cluster centres to small apartments), rehabilitative services, and, at a lesser extent, families. The variety of recruitment settings was aimed to obtain data generalizable to the entire Italian ID/LF-ASD population.

The study has been conducted in agreement with the latest version of the Declaration of Helsinki, under the guiding principle of not violating participants' ethical values and respecting the principles of autonomy, benefit, and privacy. The participation to the study did not influence the provision of ongoing treatments. All the candidates or their legal representatives signed an informed consent in which the observational, non-interventional nature of the study was explained. The purposes of the study were directly elucidated to those participants able to express a consent, adapting the explanation to their cognitive skills, according to the principles expressed in the ONU convention on the rights for persons with disabilities regarding self-determination and self-representativeness (Nations, 2016). According to the current legislation on Personal Data Protection, an informed consent that allowed the use of personal data had to be signed for each participant, and anonymity was guaranteed.

The entire sample underwent to a complex anamnestic evaluation implying the collection of demographics, psychosocial, and clinical information via a semi-structured interview developed ad hoc for the present study. The interview included information regarding the physiological anamnesis with specific focus on early developmental events during pregnancy and in the first stages of life, also encompassing the achievement of developmental milestones. The personal and familial histories for medical and psychiatric issues were investigated. Information about previous psychopharmacological and non-pharmacological interventions was collected. The eventual psychiatric diagnoses formulated prior to the participation to the study were registered, in order to compare them with the diagnoses resulted from the overall assessing procedure of the study (the diagnosis obtained with SPAIDD-M and a final diagnosis integrating both clinical judgement and the outcomes of the standardized assessment).

The probands had the possibility to participate to their own evaluation procedure and had the possibility to integrate proxy's information, for example giving further explanations regarding feelings and thoughts.

The assessments were conducted in a quiet, private room for the interview, which lasted approximately one to two hours for each participant. The assessment scheme was the following: (a) general interview for collecting demographic data; (b) clinical assessment; (c) administration of psychopathology assessment tools.

The full study protocol was completed for 141 participants (the 68.4% of the sample), directly evaluated by the CREA team. The remaining 65 participants received variable combinations of the tools convenient to the external evaluators.

2.3 Assessment tools

The study protocol included the following assessing instruments for the evaluation of mood disorders:

- SPAIDD-M 1.2
- DASH-II
- DSM-5 criteria for Major Depressive Episode, Mania and Hypomania.

SPAIDD-M

The SPAIDD-M used for the final draft of this study was the 1.2 version. It is organized in three sections. *Section A* is constituted by 46 dichotomous questions regarding a variety of behaviors and symptoms (e.g. appetite, sleep, mood, etc.) possibly associated to MDs. Three different patterns and labels underline the mood polarity of symptoms and behaviors, in order to facilitate the evaluator in the formulation of questions. The last three items of the section refer to clinical specifiers (catatonic and psychotic symptoms). The instructions for the compilation of the instrument stress the fundamental concept that the SPAIDD-M explores the *entire life-span*, but behaviors and symptoms described in the questionnaire have to be present for circumscribed period/s in a significant different way from the baseline functioning of the proband. The evaluator is recommended to underline and repeat this concept and to help the informant/s in making differences with baseline. Noteworthy, 10 items (from 24 to 33) are considered overlapping between the depressive and manic polarities, according to the data from the literature.

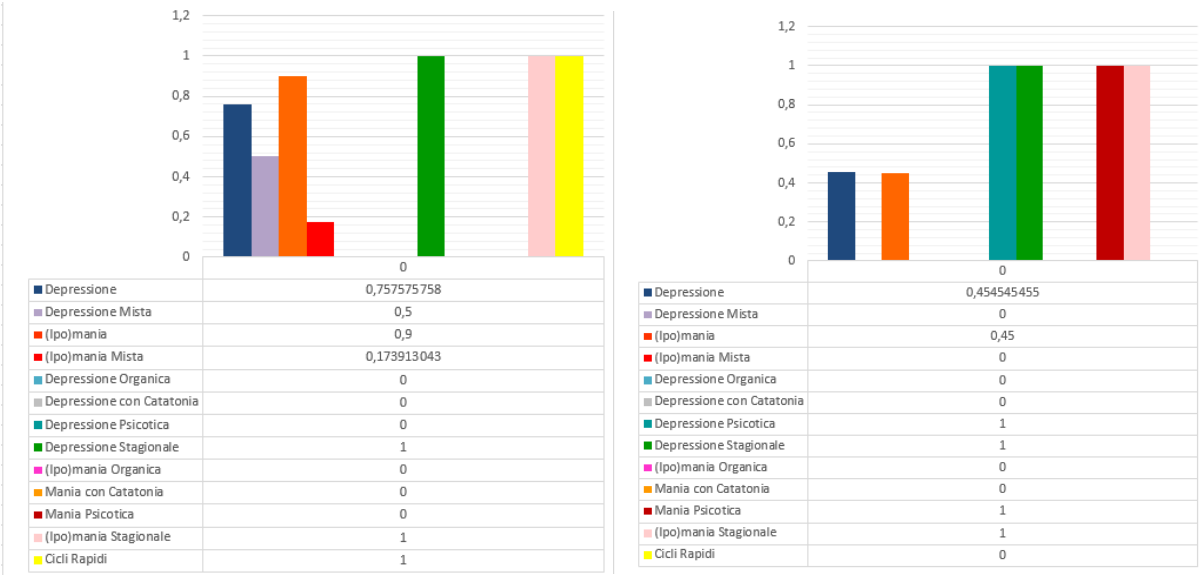
Section B is made of 10 items encompassing the chronological and course specifiers for the diagnosis and differentiation of DDs. A template for the registration of non-overlapping excitatory symptoms eventually present during depression is included for the diagnosis of MDE with mixed features. Given the difficulties in clearly detecting mixed features, the compilation of the mixed features template is considered optional. Section B explores the duration and qualitative criteria for MDE, persistent depressive disorder (PDD), premenstrual dysphoric disorder and substance/medication-induced depressive disorder or depressive disorder due to another medical condition (the two latter considered together). There are also questions regarding seasonal course pattern, psychotic and catatonic features of depression. The last question of the section investigates the severity of symptoms and related functional impairment comparing to baseline.

Section C has a structure similar to section B and the 10 questions allow the chronological and severity differentiation among mania, hypomania and cyclothymic disorder. The specifiers encompassed are the seasonal pattern of the disease, psychotic and catatonic features, rapid cycling, relationship of symptoms with substances, medications or medical illnesses and mixed features. Similar to section B, an optional template for non-overlapping depressive symptoms presenting during (hypo)mania is provided.

The score for each item is dichotomous (zero or one) according to the presence or absence of the symptom/behavior described. The 65 items are entered in a complex scoresheet specifically developed to adapt behavioral and symptoms equivalents to DSM-5 criteria for DDs and BDs. The scoresheet allows a definite categorical diagnosis among the following: MDD, PDD, premenstrual dysphoric disorder, substance/medication-induced depressive disorder or depressive disorder due to another medical condition

(organic depression), BD type I, BD type II, cyclothymic disorder, BD otherwise specified (short duration hypomania, hypomania with insufficient symptoms, hypomania without depression, short duration cyclothymia) and substance/medication-induced BDI or II or due to another medical condition (organic BDI and II). The scoresheet also provides a graphic representation of symptomatic dimensions based on the relative scores obtained for depression, (hypo)mania, mixed depression and mixed (hypo)mania. This is the first step toward the development of an instrument able to integrate both categorical and dimensional perspectives. **Figure 1** represents two examples of the graphics produced along with the scoresheet. The graphics also give indications regarding the full meeting of the main clinical and course specifiers. The mean time for the administration of the SPAIDD-M was 30 minutes.

Figure 1. Two examples of graphics produced with the SPAIDD-M 1.2 score sheet.



DASH-II

DASH-II is an 84-item screening instrument developed in 1991 and subsequently improved by using the DSM classification system and the authors' past experience (Matson, 1995). It is mostly aimed to detect major psychiatric disorders in individuals with moderate-to-profound ID. The full description of the instrument and its psychometric properties have already been drawn in chapter 1.7. Each item describes a variety of symptoms and behaviors commonly found in individuals with lower cognitive abilities, including PBs. Their relevance is estimated by means of a combined score of their frequency, severity and duration. The symptoms are clustered to describe psychiatric syndromes and are considered clinically significant when individual clusters overcome a cut-off value.

The validity of the subscales for depression and mania have been tested (Matson et al., 1999, Matson and Smiroldo, 1997) comparing to DSM criteria. The mean time for the administration was 20 to 30 minutes.

DSM-5 CRITERIA FOR MAJOR DEPRESSION AND (HYPO)MANIA

The symptomatic criteria for the MDE, hypomanic and manic episode were evaluated by two clinical psychiatrists, expert in the psychiatric diagnosis in intellectually disabled and ASD persons. The use of DSM criteria by fully trained professionals in the field of ID would inevitably account for the suggestions and adaptations provided by Diagnostic Criteria for Learning Disability (DC-LD) (Psychiatrists, 2001) and Diagnostic Manual - Intellectual Disability (DM-ID-2) (Fletcher et al., 2016) developed by the American Psychiatric Association and the Royal College of Psychiatrists, respectively. This is important to be emphasized, as it is possible that the sensitivity of the clinical diagnosis could be different (probably higher) than in conventional psychiatric settings, but it could also have to be considered as a possible bias source. DSM-5 criteria have been chosen as the comparator for the validity of the SPAIDD-M diagnosis for the overall sample but mostly for persons with mild and moderate ID, since most literature suggested that DSM criteria are able to detect comorbid PDs in these subpopulations (Two separate validation procedure are provided).

A special session for the evaluation of inter-rater reliability was performed. A clinical case was told to a group of different professionals usually working with ID and LF-ASD and including psychiatrists, psychologists, nurses and educators. They were asked to complete SPAIDD-M according to the information given. They were blind to the purpose of the assessing session and blind one to each other for the completion of SPAIDD-M. A CREA researcher compiled the respective scoresheets and a separate section of the database for the comparisons needed for inter-rater reliability testing.

2.4. Development of SPAIDD-M 1.2

At first, a systematic mapping of the literature regarding MDs in ID and LF-ASD was conducted in order to acquire complete information regarding the presentation and course peculiarities of depressive and bipolar illnesses in this population. The mapping also encompassed the evaluation of already existing assessing instruments for MDs and related studies to explore their strengths and weaknesses. The synthesis of this work can be found in chapters 1.6 and 1.7.

A first version of SPAIDD-M was produced, *SPAIDD-M 1.1*. The main structure of the tool and items followed the conceptual and practical organization of the DM-ID 2 and DC-LD. The results of the literature research were used to expand items. A scoresheet and a database were developed.

SPAIDD-M 1.1 version was a 35-item tool and included a list of mood symptoms and behavioral equivalents pertaining depression and (hypo)mania. It was simple and rapid to be used. The first 27 items regarded observable symptoms and behaviors, while the last 8 items allowed the diagnostic framing of MDD, Dysthymic Disorder, BD I and II, Cyclothymic Disorder according to chronological criteria and the specification of premenstrual symptoms and syndromic pictures related to substances, medications and general medical conditions.

A pilot experimentation with 120 adults with ID recruited among those attending the residential and clinic-rehabilitative facilities of the San Sebastiano Foundation in Florence was performed and the results were

presented in national and international conferences (Vannucchi et al., 2017b). All the participants underwent a complex anamnestic, cognitive and psychopathological evaluation, through the administration of structured and semi-structured assessing instruments (WAIS-III, ISTORIA, SPAIDD-G 1.8 version, SPAIDD-M 1.1; 26 patients were also evaluated with DASH-II). SPAIDD-M 1.1 showed good psychometric properties. The internal consistency was high with a Chronbach's alfa coefficient of 0,81. The Cohen's k=0,76 demonstrated good inter-rater reliability. The concordance with the subscales for mood symptoms of the DASH-II was 98%. The overall prevalence of MDs was around 36%. MDD rate was near to 17%, BD type I and II had a 9.3% prevalence rates, respectively, cyclothymic disorder was 3.7%, dysthymic disorder 2.8% and premenstrual increase of the symptoms were identified in around the 2% of the sample. These rates resulted much higher than previously reported in the majority of studies. SPAIDD-M 1.1 was hypothesized to be much more sensitive in identifying atypical presentations and this result confirmed the experimental hypothesis that intellectual developmental disorder would be associated to higher vulnerability for the development of MDs. However, it is also possible that such high rates could be the result of low specificity of the tool. Moreover, other issues emerged:

- A good face validity was limited to the symptomatic/behavioral items, whereas chronological and course specifiers' items resulted complex and a possible source of bias. The full range of specifiers provided by DSM-5 was not encompassed.
- MDs diagnoses were based on overcoming the minimum cut-off number of symptoms for both depression and (hypo)mania established by DSM criteria. In the SPAIDD-M 1.1 the cut-off number was disrespectful to the actual correspondence of symptomatic and behavioral equivalents to DSM-5 criteria. In fact, it is possible that more than one behavior is related to one unique criterion. This limitation was a potential source of reduced specificity.
- In the cluster system developed for DSM-IV-TR and then revised for DSM-5 by Michael First and colleagues (First, 2014, First et al., 2003) more symptoms and behaviors clustered with MDs, especially with depression. Some of these symptoms and behaviors had been ruled out by SPAIDD-M 1.1, in order to reduce the time required for the interview. These exclusions would be argued to affect the sensitivity, especially in those patients with lower communicative and cognitive skills and very limited behavioral repertoires.
- The differential diagnosis among different MDs was based on chronological items defining the illness course according to DSM conceptualization. This approach arose problems in the differential diagnosis between type I and II BD. Moreover, the BDs otherwise specified were not diagnosable, even if they represent a residual category often used in clinical practice and administrative registries. The lack of the residual category pertaining to the so-called soft bipolar spectrum seemed to potentially lead to underestimation of BDs in favour of DDs.
- Some problems were found with the reliability of items related to reduced pleasure, feelings of guilt and racing thoughts, probably due to the difficulties to find reliable behavioral equivalents of those cognitive symptoms.

In order to improve the specificity and implement the content validity and reliability, SPAIDD-M 1.1 was revised. The revised version, *SPAIDD-M 1.2*, consisted in some face, conceptual and content changes. The face validity was revised twice as a first draft arose some perplexities and completion challenges by most external evaluators. The changes are summarized as follows:

- The symptomatic/behavioral items' section was implemented by the addition of items accounting for all the symptoms indicated in the fundamental clusters designed for DSM-IV-TR (First et al., 2003). Adaptations were provided according to the differences between DSM-IV-TR and DSM-5. In this process, the adaptation of the items continued integrating the suggestions of the literature regarding atypical manifestations and behavioral equivalents of MDs in PwID and LF-ASD. For example, irritable mood characterizing depression is usually considered a counterpolar symptom in persons with typical neurodevelopment as well as aggressiveness. The ID-related literature showed that these are commonly associated symptoms, sometimes prominent, in most cases of depression in PwID. Thus, we considered them as overlapping symptoms and possibly clustering with both depression and (hypo)mania. Moreover, the sentencing of some items was ameliorated in order to stress the underlying relationship with MDs. For example, the SPAIDD-G item generically related to sleep problems was decomposed in two items specifically addressing to insomnia and reduced need for sleep, respectively.
- Each item was grouped with other items to univocally cluster with one DSM criterion according to its main psychopathological link with the criterion. This adaptation procedure may show some limitations, for example, in different patients, withdrawal may be linked to hypobulia, co-occurring anxiety or both, and the attribution of the behavior to a cluster or another could appear arbitrary. Therefore, we speculated that in presence of a full-blown mood syndrome, this limitation should have minor effects on the reliability of the diagnosis, while it could have some kind of impact in milder forms. Independently of the number of items clustering with one criterion, the positivity for the criterion was defined by the presence of at least one item of the group.
- In order to differentiate hypomania and mania, a "severity item" that summarizes DSM-5 criterion C for mania was added. The presence of psychotic symptoms during mania also indicated a BD type I diagnosis.
- The sentencing of the chronological criteria for PDD, cyclothymic disorder and premenstrual dysphoric disorder was also refined along with a differential clustering of symptoms according to the adaptation of their specific DSM-5 criteria.
- Further items encompassing important clinical and course specifiers were added or refined. SPAIDD-M 1.2 included items for psychotic features, catatonic features, seasonal pattern, rapid cycles and mixed features. As described above, the mixed features specifier has been adapted by excluding those items/symptoms the literature demonstrated not to be counterpolar in persons with ID and LF-ASD.

At the end of the experimentation of SPAIDD-M 1.2, some issues remain still open:

- We were not able to find univocal and reliable equivalents for racing thoughts in mania, thus in this stage the related DSM criterion was ruled out with a possible impact on the underdiagnosis of BD type I and II. The

possibility of diagnosing BD otherwise specified, namely hypomania with insufficient symptoms, may help in reducing the underestimation of bipolar conditions.

- The tool does not allow the differential diagnosis with schizophrenia spectrum disorders and some iatrogenic clinical pictures.
- The attempt to produce behavioral equivalents of feelings of guilt, unworthiness and low self-esteem has been made but the reliability could be questionable.
- The previous version of the SPAIDD-M was rapid and easy to be performed. This new version is longer, and this could affect the speed of administration and its applicability in clinical practice in general psychiatry settings. Moreover, it requires a pre-existing knowledge of MDs, as well as the knowledge of DSM criteria. The lack of these prerequisites may potentially affect the correct administration of the instrument. This aspect becomes particularly challenging regarding the completion of the templates related to mixed features. Not only the identification of mixed states in this population is very difficult even for expert clinicians, but also, during the training and the following support phone sessions with external evaluators, some professionals struggled with the basic concepts. This is the reason why we decided to perform the analyses regarding mixed features only accounting for a part of the evaluations (175 participants), mainly those made by the psychiatrists of the CREA team. This problem obviously challenges the feasibility and the generalizability of this component of the evaluation.

2.5 Statistical analyses

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

For comparisons between groups, χ^2 test for categorical variables and ANOVA and F-variance test for continuous variables were used. For the analyses relative to the comparisons among three groups, the Scheffè test was considered. The analyses involved many tests of statistical significance, raising the potential of type I and type II errors. Given the sample size and the number of comparisons, we reported as significant differences the results with $p < .05$.

The evaluation of the psychometric properties of the tool involved different analyses. For the evaluation of internal consistency, we used a reliability test with the calculation of the Cronbach'α coefficient. The inter-rater reliability was evaluated with a correlation analysis and the calculation of Cohen's K coefficient. For the validity criterion, two ANOVA analyses were performed including the first the SPAIDD-M categorical diagnosis of MDE as the grouping factor, and the mean relative scores of the depressive items clustering the 9 DSM-5 criteria for the MDE as well as total mean score for the MDE; the second included the categorical diagnosis of (hypo)mania made with the SPAIDD-M and the mean relative scores of equivalents clustering with DSM-5 criteria A and B, and the relative mean total score for the (hypo)manic episode.

For the realization of the pattern matrix of the factorial analysis we used a principal component analysis, for the extraction, and oblimin with Kaiser normalization, for the rotation.

Test-retest reliability was evaluated with Person's and Spearman's correlation analyses.

Two stepwise backward procedure logistic regression models were then used to identify the predictive value of the familial and psychiatric comorbidity features for the diagnosis of BD according to the SPAIDD-M and clinical diagnoses. Odds ratios with 95% confidence intervals were used for observed associations.

SPSS 22.0 statistic pack for Windows has been utilized to create and update the database and for further statistical processing of data.

CHAPTER 3

3. RESULTS

3.1 Background features of the sample

A total of 233 probands participated to the study, including 169 (72.5%) males and 64 females (27.5%) with a mean age of 41.00 years (SD 15.93). The distribution of ID levels was the following: 66 participants had mild ID or BIF (28.3%), 88 had moderate ID (37.8%), and 79 had severe or profound ID (33.9). 83 participants also had a diagnosis of ASD (35.6%).

The socio-demographic features of the sample are summarized in **Table 2**. Comparisons of them according to 3 ID levels were made.

Table 2. Socio-demographic features and comparisons according to ID levels

Demographic and socio-economic features	**BIF/Mild ID N=66**	**Moderate ID N=88**	**Severe/Profound ID N=79**	**χ^2 or F**	**p**
Gender (M) N (%)	44 (66.7)	69 (78.4)	56 (70.9)	2.77	NS
Age, Mean (sd)	38.09 (15.18)	41.47 (15.55)	42.92 (16.80)	1.73	NS
BMI, Mean (sd)	23.05 (6.73)	23.66 (12.86)	22.36 (8.41)	.27	NS
Recruitment source N (%)					
Residential facilities	22 (33.3)	45 (51.1)	42 (53.2)	7.22	NS
Rehabilitative centers	27 (40.9)	26 (29.5)	25 (31.6)		
Families	17 (25.8)	17 (19.3)	12 (15.2)		
Adopted N (%)	2 (3.5)	1 (1.6)	3 (4.7)	.98	NS
Invalidity pension N (%)	55 (98.2)	63 (98.4)	62 (96.9)	.42	NS
Employed N (%)	16 (28.1)	8 (3.1)	2 (3.1)	15.73	<.001
Problems with justice N (%)	5 (8.8)	0 (0.0)	1 (1.7)	7.61	.022
Provenance N (%)					
Urban, big city	16 (28.1)	22 (35.5)	13 (22.0)	3.27	NS
Periphery, small city	36 (63.2)	33 (53.2)	38 (64.4)		
Rural	5 (8.8)	7 (11.3)	8 (13.6)		
Familial economic level N (%)					
Low income	10 (17.5)	4 (7.0)	14 (24.1)		

Medium income	36 (63.2)	47 (82.5)	31 (53.4)	11.53	.021
High income	11 (19.3)	6 (10.5)	13 (22.4)		
Educational Level N (%)					
None	1 (1.9)	4 (7.1)	11 (19.0)	20.53	.008
Primary	7 (13.0)	7 (12.5)	12 (20.7)		
Secondary	22 (40.7)	25 (44.6)	9 (15.5)		
Tertiary	24 (44.4)	20 (35.7)	9 (15.5)		
Educational support	49 (87.5)	49 (86.0)	47 (85.5)	.11	NS
Quality of familial relationships N (%)					
Low	17 (30.9)	7 (12.1)	12 (21.4)	6.11	NS
Medium	20 (36.4)	28 (48.3)	25 (44.6)		
High	18 (32.7)	23 (39.7)	19 (33.9)		
Friendships N (%)					
None	10 (17.5)	17 (28.8)	39 (65.0)	34.71	<.001
Few	30 (52.6)	29 (49.2)	19 (31.7)		
Normal	17 (29.8)	13 (22.0)	2 (3.3)		
Romantic relationships N (%)	8 (14.3)	9 (15.3)	1 (1.7)	7.38	.025

No differences were detected regarding gender distribution, mean age and BMI.

Similarly, the three subgroups did not report significant differences in the other socio-demographic parameters explored except for occupational status and previous justice problems, resulting higher among BIF/Mild ID individuals. The achievement of higher educational levels was significantly different among the three subgroups with severe to profound ID individuals reporting shorter scholastic pathways despite no differences in educational supports. Differences in the distribution of the family economic status were evidenced.

No differences emerged in the quality of familial relationships, whereas moderate to profound ID individuals showed significantly poorer social adjustment comparing to the other two subgroups.

3.2 Medical, family and psychiatric history of the sample

The comparisons regarding physiological and familial features according to ID levels are summarized in **Table 3**.

The physiological parameters explored included age of the mother and father at birth, the anamnesis of pregnancy and delivery, early development including first physiological acts, psychomotor, autonomous locomotion and language development. The considered variables about pregnancy and delivery did not differentiate the three subgroups. The comparisons of physiological variables showed severe to profound ID to be associated to significantly higher rates of abnormalities in post-delivery physiological acts (42.4%) and delayed psychomotor, locomotion and language developments (76.3%, 76.9%, 92.3%, respectively).

Table 3. Physiological and familial features of the sample and comparisons according to ID levels

Physiological features	**BIF/Mild ID N=66**	**Moderate ID N=88**	**Severe/Profound ID N=79**	**χ^2 or F**	**p**
Age of the mother at birth, Mean (sd)	30.65 (7.30)	31.68 (5.15)	30.67 (6.24)	.16	NS
Age of the mother at birth, Mean (sd)	35.41 (8.51)	31.63 (9.16)	34.20 (6.47)	.99	NS
Pregnancy N (%)					
Problematic course	9 (27.3)	5 (13.9)	7 (21.2)	1.90	NS
At term	28 (84.8)	30 (83.3)	22 (66.7)	4.56	NS
Preterm	3 (9.1)	5 (13.9)	8 (24.2)		
Post-term	2 (6.1)	1 (2.8)	3 (9.1)		
Delivery N (%)					
Eutocic	15 (46.9)	23 (63.9)	17 (51.5)	10.45	NS
Dystocic	7 (21.9)	9 (25.0)	12 (36.4)		
Planned caesarean section	5 (15.6)	3 (8.3)	0 (0.0)		
Urgency caesarean section	5 (15.6)	1 (2.8)	4 (12.1)		
Physiological developmental variables N (%)					
First physiological acts (abnormal)	7 (21.9)	5 (13.9)	14 (42.4)	7.70	.021
Breast feeding	21 (67.7)	25 (78.1)	21 (70.0)	.94	NS
Delayed psychomotor development	14 (40.0)	17 (45.9)	29 (76.3)	11.35	.003
Delayed autonomous locomotion	17 (48.6)	16 (40.0)	30 (76.9)	11.80	.003
Delay or absence of language development	31 (88.6)	27 (69.2)	36 (92.3)	8.48	.014
Familial history N (%)					
Familial history for neuropsychiatric disorders	14 (29.2)	13 (30.2)	7 (16.3)	2.78	NS
Familial ASD	3 (6.3)	2 (4.8)	2 (4.7)	.15	NS
Familial ID	11 (22.9)	6 (14.3)	6 (14.0)	1.66	NS
Familial history for psychiatric disorders	28 (56.0)	22 (45.8)	15 (32.6)	5.31	NS (.070)
Familial history for medical illness	26 (61.9)	22 (51.2)	17 (48.6)	1.61	NS
Familial autoimmune diseases	7 (15.9)	4 (9.3)	4 (11.4)	.914	NS

The comparisons regarding the familial load for medical illness, neuropsychiatric and psychiatric conditions did not evidence significant differences among the three ID subgroups considered. However, severe/profound ID individuals showed lower rates of familial psychiatric load (32.6% vs. 56.0% in BIF/mild ID and 45.8% in moderate ID, χ^2=5.31), near to the statistical significance (p=.070).

The main medical illnesses were compared among the three subgroups. These comparisons are shown in **Table 4**. Specific genetic analyses had been performed in a relative minority of the patients, without significant

differences among the three subgroups, and a specific genetic cause related to ID had been identified in proportions varying from 28.3% in BIF/mild ID participants to 17.6% of severe/profound ID.

Table 4. Medical comorbidity features of the sample and comparisons according to ID levels

Medical health N (%)	BIF/Mild ID N=66	Moderate ID N=88	Severe/Profound ID N=79	χ^2	p
Genetical analyses	18 (32.7)	24 (40.0)	18 (34.0)	.77	NS
Genetic syndrome ID-related	15 (28.3)	13 (21.7)	9 (17.6)	1.73	NS
Specific genetic syndromes N (%)					
Down's Syndrome	8 (15.1)	7 (12.1)	3 (6.0)	22.34	NS
Rett's Syndrome	0 (0.0)	0 (0.0)	1 (2.0)		
Prader-Willi Syndrome	1 (1.9)	0 (0.0)	1 (2.0)		
Williams' Syndrome	1 (1.9)	0 (0.0)	0 (0.0)		
Cri du chat syndrome	0 (0.0)	0 (0.0)	2 (3.9)		
Klinefelter's Syndrome	0 (0.0)	2 (3.4)	0 (0.0)		
Epileptic encephalopathy	0 (0.0)	1 (1.7)	0 (0.0)		
Neurometabolic disorder	0 (0.0)	0 (0.0)	1 (2.0)		
Other genetic conditions	5 (9.4)	3 (5.2)	1 (2.0)		
Medical illness N (%)					
General medical comorbities	38 (63.3)	53 (72.6)	55 (79.2)	10.45	NS
Epilepsy	4 (6.7)	18 (25.4)	44 (36.2)	15.81	<.001
Gastrointestinal disturbances	8 (13.3)	13 (18.8)	20 (29.0)	5.01	NS (.082)
Diabetes	3 (5.0)	5 (4.4)	3 (4.3)	.04	NS
Obesity	11 (18.6)	16 (23.5)	7 (10.1)	4.38	NS
Immunity dysreactivity	19 (39.6)	12 (21.4)	7 (14.0)	9.12	.010
Motor disabilities	13 (21.7)	11 (15.7)	26 (37.7)	9.46	.009
Cardiovascular diseases	6 (10.0)	7 (10.4)	8 (11.6)	.09	NS
Sensory impairments	2 (3.3)	3 (4.4)	10 (14.5)	7.20	.027

The presence of epilepsy, gastrointestinal disturbances, diabetes, obesity, immunity disreactivity including allergies and autoimmune diseases, motor disability, cardiovascular diseases and sensory impairments was investigated. One or more medical illnesses were identified in the 72.3% of the overall sample, indicating a high medical burden in ID comparing to the general population and according to the mean age of the sample. The three subgroups did not show significant differences in the rates of general medical comorbidities, but differences were detected considering specific illnesses. The rates of epilepsy and motor disabilities showed increasing rates directly proportional to the severity of ID, with the highest rate of 36.2% and 37.7% in severe/profound ID individuals, respectively (χ^2=15.81, p<.001 for epilepsy, χ^2=9.46, p=.010). Gastrointestinal disturbances showed a similar trend not achieving statistical significance. Sensory impairments resulted more

frequent in severe/profound ID, with 14.5% prevalence rate comparing to 3.3% and 4.4% in BIF/Mild ID and moderate ID subgroups (χ^2=7.20, p=.027). By the contrary, immunity disreactivity showed a higher prevalence rate in BIF/mild ID (39.6%) comparing to decreasing rates in moderate and severe/profound ID (21.4% and 14.0%, respectively; χ^2=9.12, p=.010

Table 5 summarizes the comparisons of psychiatric diagnoses and related variables according to ID levels. The comparisons have been performed considering the diagnoses made before the study (external diagnosis) and those resulted from the complex diagnostic study protocol (internal diagnosis). The first interesting result was that severe/profound ID individuals had significant lower rates of co-occurring psychiatric disorders according to the external diagnosis, based on as usual diagnostic process (χ^2=22.18, p<.001). This difference was not confirmed by the study diagnostic protocol and internal clinical diagnosis (χ^2=1.79, not significant), and severe/profound ID individuals showed rates similar to BIF/Mild ID and moderate ID subjects. The analysis of the degree of diagnostic concordance evidenced, as expected, the highest levels of concordance in BIF/mild ID subjects, whereas the rates of diagnostic divergence were similar in moderate and severe/profound ID probands (25.4% and 22.8%, respectively; χ^2=11.85, p=.019).

ASD showed similar rates across the three subgroups, ranging from 31.8% in BIF/mild ID and 39.2% in severe/profound ID individuals.

The three subgroups did not show statistically significant differences in the prevalence of the majority of psychiatric disorders, specifically both depressive and bipolar disorders. Anxiety disorders showed the highest prevalence rates in BIF/mild ID according to both external and internal diagnosis, although the prevalence was doubled according to the latter diagnostic pathway (17.2% vs. 34.1%). Similarly, the prevalence of anxiety disorders resulted doubled in the moderate ID subgroup according to external and internal diagnosis (9.1% vs. 22.6%), although the greatest effect of the diagnostic process affected the severe/profound ID group, with rates about 5-fold higher (from 1.3% to 7.1%). No differences emerged regarding the specific anxiety disorders. However, panic disorder showed higher rates in BIF/mild ID subjects compared to the two other subgroups, although not reaching the statistical significance (χ^2=5.66, p=.059).

Schizophrenia Spectrum Disorders (SSDs) showed higher rates in both BIF/mild ID and moderate ID compared to severe/profound ID according to the external diagnosis (χ^2=9.81, p=.007). The internal diagnosis did not reveal this difference. Interestingly, most individuals in all the three subgroups were reframed from the so-called graft psychosis and behavioral abnormalities category to schizoaffective disorder. According to the internal diagnosis, the co-occurrence of another neurodevelopmental disorder showed an increasing prevalence gradient proportional to the increasing severity of ID, from 42.2% in BIF/mild ID, to 57.1% and 82.9% in moderate and severe/profound ID, respectively (χ^2=13.53, p=.001). This significant gradient specifically regarded the prevalence rates of ASD (χ^2=13.74, p=.001).

Table 5. Psychiatric comorbidity features of the sample, other related variables and treatments: comparisons according to ID levels

Mental health N (%)		BIF/Mild ID N=66	Moderate ID N=88	Severe/Profound ID N=79	χ^2 or F	p
Psychiatric comorbidity	E	38 (60.3)	48 (62.3)	22 (28.2)	22.18	<.001
Psychiatric comorbidity	I	42 (64.6)	54 (69.2)	46 (59.0)	1.79	NS
Diagnostic concordance external/internal diagnosis N (%)						
Complete divergence		4 (7.4)	16 (25.4)	13 (22.8)	11.85	.019
Partial concordance		15 (27.8)	21 (33.3)	10 (17.5)		
Psychiatric comorbidity N (%)						
ASD		21 (31.8)	31 (35.2)	31 (39.2)	.87	NS
Anxiety disorders	E	11 (17.2)	7 (9.1)	1 (1.3)	11.25	.004
	I	15 (34.1)	12 (22.6)	2 (7.1)	7.0	.030
Panic Disorder	E	4 (6.3)	2 (2.6)	1 (1.3)	2.94	NS
	I	7 (15.9)	2 (3.8)	1 (3.6)	5.66	NS (.059)
GAD	E	4 (6.3)	5 (6.5)	0 (0.0)	5.20	NS (.074)
	I	7 (15.9)	6 (11.5)	0 (0.0)	4.72	NS
OCD-related disorders	E	8 (12.5)	6 (7.8)	3 (3.8)	3.68	NS
	I	7 (16.3)	5 (10.0)	3 (10.0)	1.03	NS
Schizophrenia spectrum disorders	E	10 (15.9)	9 (11.7)	1 (1.3)	9.81	.007
	I	3 (7.0)	8 (15.4)	1 (3.4)	3.58	NS
Schizophrenia	E	3 (4.7)	6 (7.8)	0 (0.0)	1.14	NS
	I	0 (0.0)	1 (1.9)	0 (0.0)	1.38	NS
Schizoaffective disorder	E	1 (1.6)	1 (1.3)	0 (0.0)	11.25	.004
	I	3 (7.0)	6 (11.5)	0 (0.0)	3.58	NS
Graft psychosis and behavioral abnormalities	E	9 (14.1)	4 (5.2)	2 (2.6)	7.79	.020
	I	0 (0.0)	0 (0.0)	0 (0.0)		
Eating disorders	E	2 (3.1)	1 (1.3)	3 (3.8)	.99	NS
	I	3 (7.0)	3 (6.1)	3 (10.7)	5.31	NS (.070)
Anorexia	E	2 (3.1)	0 (0.0)	0 (0.0)	4.89	NS
	I	2 (4.7)	0 (0.0)	0 (0.0)	3.64	NS
Bulimia	E	1 (1.6)	0 (0.0)	0 (0.0)	2.42	NS
	I	1 (2.3)	0 (0.0)	0 (0.0)	1.81	NS
BED	E	1 (1.6)	0 (0.0)	2 (2.6)	1.91	NS
	I	2 (4.7)	3 (6.1)	2 (7.1)	.20	NS
Depressive Disorders	E	3 (4.7)	3 (3.9)	2 (2.6)	.47	NS
	I	10 (15.4)	12 (15.6)	14 (18.4)	.31	NS
MDD	E	3 (4.7)	3 (3.9)	0 (0.0)	3.50	NS
	I	8 (12.1)	10 (11.4)	12 (15.2)	.59	NS
PDD	E	0 (0.0)	0 (0.0)	1 (1.3)	1.82	NS
	I	0 (0.0)	3 (3.9)	2 (2.6)	2.45	NS
Bipolar Disorders	E	9 (14.3)	9 (11.7)	7 (9.0)	.97	NS
	I	16 (25.0)	26 (33.8)	19 (25.0)	1.89	NS
BD I	E	6 (9.4)	3 (3.9)	5 (6.5)	1.75	NS

	I	12 (18.5)	11 (14.3)	11 (14.5)	.58	NS
BD II	E	1 (1.6)	0 (0.0)	1 (1.3)	1.11	NS
	I	2 (3.1)	7 (9.1)	2 (2.6)	4.08	NS
Cyclothymic Disorder	E	0 (0.0)	0 (0.0)	0 (0.0)		
	I	1 (1.5)	1(1.3)	0 (0.0)	1.10	NS
BD otherwise specified	E	2 (3.2)	5 (6.5)	1 (1.3)	3.04	NS
	I	1 (1.5)	6 (7.8)	5 (6.6)	2.91	NS
Other ND	E	22 (33.8)	28 (36.4)	26 (33.3)	.18	NS
	I	19 (42.2)	32 (57.1)	29 (82.9)	13.53	.001
ASD	E	19 (29.2)	26 (33.8)	25 (32.1)	.34	NS
	I	15 (33.3)	32 (57.1)	26 (74.3)	13.74	.001
ADHD	E	4 (6.3)	4 (5.2)	2 (2.6)	1.20	NS
	I	7 (16.3)	8 (14.8)	6 (19.4)	.30	NS
Impulse Control Disorders	E	4 (6.3)	8 (10.4)	6 (7.7)	.84	NS
	I	4 (9.3)	10 (20.0)	8 (27.6)	4.14	NS
ODD	E	2 (3.1)	4 (5.2)	3 (3.8)	.40	NS
	I	4 (9.3)	6 (12.2)	6 (20.7)	2.03	NS
Addiction-related Disorders	E	3 (4.7)	1 (1.3)	0 (0.0)	4.49	NS
	I	4 (9.3)	1 (2.0)	0 (0.0)	4.61	NS
Personality Disorders	E	7 (10.9)	6 (7.8)	1 (1.3)	5.87	NS (.053)
	I	14 (32.6)	10 (19.6)	7 (25.0)	2.07	NS
PDs Cluster A	E	3 (4.7)	2 (2.6)	0 (0.0)	3.52	NS
	I	4 (9.3)	3 (6.0)	2 (7.1)	.37	NS
PDs Cluster B	E	4 (6.3)	1 (1.3)	1 (1.3)	4.18	NS
	I	6 (14.0)	3 (6.0)	2 (7.1)	1.94	NS
PDs Cluster C	E	2 (3.1)	3 (3.9)	0 (0.0)	2.92	NS
	I	8 (18.6)	8 (16.3)	5 (17.9)	.09	NS
Treatments and related variables N (%)						
Psychiatric hospitalizations		12 (20.7)	10 (15.4)	3 (4.8)	6.74	.034
Number of hospitalizations, Mean (SD)		.52 (1.55)	.57 (1.75)	.19 (1.02)	1.19	NS
Suicide attempts		7 (11.9)	1 (1.5)	0 (0.0)	12.61	.002
Non-pharmacological treatments		48 (81.4)	55 (79.7)	48 (76.2)	.52	NS
Psychotherapy		30 (50.8)	18 (26.1)	2 (3.2)	35.83	<.001
Structured education		40 (67.8)	51 (73.9)	38 (60.3)	2.78	NS
Behavioral therapy		12 (20.3)	29 (29.0)	22 (35.5)	3.43	NS
Electroconvulsive Therapy		0 (0.0)	0 (0.0)	0 (0.0)		
Other treatments*		23 (39.7)	22 (31.9)	23 (36.5)	.85	NS
Psychopharmacological treatments		34 (56.7)	52 (75.4)	50 (78.1)	8.09	.018
Antidepressants (all)		18 (30.0)	18 (26.1)	14 (21,9)	1.07	NS
SSRI		11 (18.3)	15 (21.7)	7 (10.9)	2.83	NS
TCA		7 (11.7)	0 (0.0)	2 (3.1)	10.34	.006

Other antidepressants	6 (10.0)	6 (8.7)	6 (9.4)	.07	NS
Anticonvulsants	22 (36.7)	36 (52.2)	37 (57.8)	5.91	NS (.052)
Lithium	6 (10.0)	5 (7.2)	0 (0.0)	6.24	.044
Antipsychotics (all)	25 (41.7)	41 (59.4)	31 (33.2)	4.17	NS
FGA	14 (23.3)	15 (21.7)	13 (33.2)	.17	NS
SGA	22 (36.7)	39 (56.5)	27 (42.2)	5.55	NS (.062)
BDZ	17 (28.3)	26 (37.7)	26 (40.6)	2.21	NS
Stimulants	2 (3.3)	1 (1.4)	0 (0.0)	2.26	NS
Adverse psychiatric effects to antidepressants	7 (38.9)	7 (41.2)	5 (35.7)	.10	NS
Irritability AD	5 (27.8)	5 (29.4)	3 (21.4)	.27	NS
(Hypo)manic switch AD	3 (16.7)	2 (11.8)	1 (7.1)	.67	NS
Mood instability AD	4 (22.2)	3 (17.6)	0 (0.0)	3.42	NS
Resistance to AD	1 (5.6)	0 (0.0)	0 (0.0)	1.76	NS
Adverse effects to antipsychotics	15 (65.2)	22 (55.0)	16 (51.6)	1.05	NS
Flattening/depressed mood AP	9 (40.9)	9 (22.5)	5 (16.1)	4.43	NS
Akathisia AP	6 (27.3)	3 (7.5)	2 (6.5)	6.61	.037
EPS AP	10 (45.5)	9 (22.5)	8 (25.8)	3.87	NS
Metabolic effects and increased weight	8 (34.8)	16 (40.0)	8 (25.8)	1.57	NS

*Other non-psychopharmacological treatments also include psychomotor and logopedic interventions, ergotherapy and similar treatments E: external diagnosis according to the diagnoses registered in the archives, medical or administrative records or reported by proxies. I: internal diagnosis combining the structured assessment and clinical judgment. ASD: Autism Spectrum Disorder; GAD: Generalized Anxiety Disorder; BED: Binge Eating Disorder; MDD: Major Depressive Disorder; PDD: Persistent Depressive Disorder; BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; ND: Neurodevelopmental Disorders; ADHD: Attention-Deficit/Hyperactivity Disorder; ODD: Oppositional-Defiant Disorder; PDs: Personality Disorders.
SSRIs: Selective Serotonin Reuptake inhibitors; TCA: Tricyclic Antidepressants; FGA: First Generation Antipsychotics; SGA: Second Generation Antipsychotics; BDZ: Benzodiazepines; AD: antidepressants; AP: Antipsychotics; EPS: extrapyramidal effects

The presence and mean number of psychiatric hospitalizations as well as a history of suicide attempts can be usually considered indirect indices of illness severity. In intellectually disabled persons, especially those with higher cognitive impairments, this consideration could not be fully appropriate. BIF/mild ID and moderate ID subjects had more frequently psychiatric hospitalizations than severe/profound ID (χ^2=6.74, p=.034), although the mean number of hospitalizations did not differ across the three subgroups. 7 BIF/mild ID participants had committed a suicide attempt (11.9%), comparing to 1 with moderate ID (1.5%) and none with sever/profound ID.

No significant differences emerged across the ID levels regarding non-pharmacological treatments with the exception of BIF/mild ID that were more frequently receiving, as expected on the basis of higher cognitive skills, psychotherapeutic support than the other subgroups (χ^2=35.83, p<.001).

All the three subgroups reported very large use of psychotropic medications, showing increasing rates from higher to lower ID levels (56.7% vs. 75.4% vs. 78.1%, in the three subgroups respectively; χ^2=8.09, p=.018). No significant differences were detected regarding specific pharmacologic classes with the exception of

anticonvulsants, employed less frequently in BIF/mild ID subjects, in contrary to lithium, showing higher rates in this subgroup compared to the other two. Second generation antipsychotics showed a prescription rate of 56.5% in moderate ID subgroups, higher than the 42,2% of severe/profound ID and the 36.7% of BIF/mild ID participants. Noteworthy, the χ^2 statistics were only about the significance for anticonvulsants and antipsychotics.

Among those ID patients reporting past or present assumption of antidepressants, the 38.8% (N=19) had suffered for their psychiatric adverse effects, namely antidepressant-induced irritability and activation (N=13, 26.5%), (hypo)manic switches (N=6, 12.2%) and increased mood instability (N=7, 14.3%). Resistance to antidepressants was reported only for one patient (2.0%). The comparisons among the three ID subgroups did not show significant differences.

53 of the 94 ID patients treated with antipsychotics (56.4%) reported adverse effects: affective flattening and antipsychotic-related depressed mood (N=23, 24.7%), akathisia (N=11, 11.8%), EPS (N=27, 29.0%) and weight gain or metabolic side effects (N=32, 34.0%). Only the rates of akathisia resulted significantly different across the three ID subgroups, being higher in BIF/mild ID (χ^2=6.61, p=.037), but it is possible that in this group akathisia was more easily detectable.

3.3 Psychometric properties of SPAIDD-M 1.2

3.3.1 Internal Consistency

The internal consistency of SPAIDD-M was evaluated via a reliability analysis including all the main 65 items of the tool. The Cronbach'α was .937. The analyses relative to each item evidenced very homogeneous values, ranging from .934 and .938. The Cronbach'α calculated for the 33 items related to mixed symptoms was lower, but acceptable (Cronbach'α=.876).

3.3.2 Inter-rater reliability

As explained in the method section, the inter-rater reliability was tested via one special session in which different professionals (psychiatrists, psychologists and professional educators) independently completed the SPAIDD-M of a single clinical case. The comparison among the individual items and categorical diagnoses according to the SPAIDD-M score sheet expressed by different evaluators indicated an acceptable inter-rater reliability. This can be considered an indirect sign of homogeneity in the attribution of absence ì/presence to the items. The inter-rater reliability of SPAIDD-M as expressed by a Cohen's K coefficient that resulted to range from .870 and .575, with a mean of .713

3.3.3 Face validity

The last version of the SPAIDD-M, more than the previous, was judged by most of the involved evaluators as sufficiently clear and easy to use. This judgment appears to be particularly related to the intelligibility of individual items of all the three section. The explanatory instruction document in attachment to the test, stressing the fundamental rules to the correct completion of the tool, has added further clarity. However, some

external evaluators found high difficulties for the completion of the mixed symptoms specifiers and symptomatic items, therefore we decided to consider for the related statistical analyses only those questionnaires directly verified by the CREA team or performed by expert psychiatrists. Indeed, some issues seemed to arise from actual difficulties in detecting specific counterpolar symptoms and behavioral equivalents in complex clinical pictures; however, it has been noted that some evaluators without a basic knowledge of mood disorders had some problems in understanding what they were asked to detect.

It has to be considered that this is the first study attempting to the conceptualization and operationalization of mixed features in ID and LF-ASD individuals.

3.3.4 Criterion validity

The criterion validity of the items related to depression have been evaluated by means of the ANOVA analysis including the SPAIDD-M categorical diagnosis of MDE as the grouping factor, and the mean relative scores of the depressive items clustering the 9 DSM-5 criteria for the MDE as well as total mean score for the MDE. As shown in **Table 6,** all the relative scores for each criterion and the total score resulted higher in the SPAIDD-M MDE diagnosed group.

Table 6. ANOVA analysis of the variance for the criterion validity of MDE in SPAIDD-M

DSM-5 MDE criteria: SPAIDD-M mean scores		**Mean (SD)**	**F**	**p**
Criterion 1	No	.14 (.17)		
Depressed mood	MDE	.47 (.21)	155.96	<.001
Criterion 2	No	.12 (.14)		
Diminished interest/pleasure	MDE	.44 (.22)	153.17	<.001
Criterion 3	No	.03 (.12)		
Weight/appetite alterations	MDE	.28 (.29)	61.05	<.001
Criterion 4	No	.06 (.18)		
Sleep disturbances	MDE	.42 (.35)	83.94	<.001
Criterion 5	No	.21 (.23)		
Psychomotor alterations	MDE	.53 (.23)	105.02	<.001
Criterion 6	No	.05 (.21)		
Fatigue/loos of energy	MDE	.64 (.48)	121.00	<.001
Criterion 7	No	.19 (.32)		
Worthlessness/guilt	MDE	.57 (.35)	70.63	<.001
Criterion 8	No	.11 (.17)		
Difficulty concentrating/doubt	MDE	.39 (.29)	67.08	<.001
Criterion 9	No	.05 (.16)		
Suicidality	MDE	.30 (.32)	46.71	<.001
Total mean score for MDE criteria	No	.12 (.08)		
	MDE	.44 (.15)	353.144	<.001

MDE: patients resulted positive with a Major Depressive Episode according to the SPAIDD-M definition
No: patients without the positivity for MDE

The validity criterion for (hypo)mania was evaluated via the ANOVA analysis considering the categorical diagnosis of (hypo)mania made with the SPAIDD-M and the mean relative scores of equivalents clustering with DSM-5 criteria A and B, and the relative mean total score for the (hypo)manic episode. Similar to MDE, the relative scores for the (hypo)manic episode criteria and the mean total relative score for all the (hypo)manic equivalents resulted higher in the group of participants diagnosed with a (hypo)manic episode by SPAIDD-M. Details can be found in **Table 7**.

Table 7. ANOVA analysis of the variance for the criterion validity of the (hypo)manic episode in SPAIDD-M

DSM-5 (hypo)manic episode criteria: SPAIDD-M mean scores		**Mean (SD)**	**F**	**p**
Criterion A	No	.31 (.27)	202.43	<.001
	Man	.86 (.16)		
Criterion B	No	.21 (.17)	185.48	<.001
	Man	.54 (.14)		
(Hypo)manic episode SPAIDD-M relative score	No	.24 (.18)	244.74	<.001
	Man	.64 (.12)		

Man: patients resulted positive with a (hypo)manic episode according to the SPAIDD-M definition
No: patients without the positivity for a (hypo)manic episode

For the factorial analysis of the full instrument, a discrimination analysis of four centroid groups' functions was carried out and equal eigenvalues were calculated. These resulted to be as follows: 10.071, 2.654, 2.328 and 2.066, corresponding respectively to the following explained variance percentages: 21.9, 5.8, 5.1 and 4.5. The four discriminating functions represent a considerable percentage of items variance, equal to 37.21.
Sample adequacy, calculated through Kaiser-Meyer-Olkin Measure, resulted to of .84, with a statistical significance of < 0.0001 (Bartlett's Test). The Wilks test showed the four discriminating functions to be statistically significant ($p < 0.001$) and to explain differences among items very well. Evaluations were therefore judged as collectable following four main standard discriminating functions, which seem to correspond to manic symptoms, depressive symptoms, non-mood related depressive symptoms, and last factor inversely correlated to anxiety (see **Table 8**).

Table 8. Factor analysis pattern matrix on SPAIDD-M items	Factor 1 Manic	Factor 2 Depressive	Factor 3 Non-mood D	Factor 4 Vs-Anxiety
SPAIDD-M Item 1: Depressed Mood	,045	**,433**	,295	-,230
SPAIDD-M Item 2: Anhedonia	,159	**,322**	**,342**	**-,382**
SPAIDD-M Item 3: Weight gain	,166	-,116	**,407**	-,139
SPAIDD-M Item 4: Insomnia	**,448**	,107	,153	-,081
SPAIDD-M Item 5: Hypersomnia	,133	,123	**,377**	,033
SPAIDD-M Item 6: Psychomotor retardation	,052	,067	**,468**	-,062
SPAIDD-M Item 7: Loss of energy/fatigue	,279	,282	**,404**	-,209
SPAIDD-M Item 8: Guilt	,263	-,199	,227	**-,345**
SPAIDD-M Item 9: Reduced participation	**,312**	**,322**	,285	-,214
SPAIDD-M Item 10: Self-injury	,282	,285	-,263	-,119
SPAIDD-M Item 11: Tendency to cry	**,314**	-,102	-,154	-,281
SPAIDD-M Item 12: Appetite alterations	,045	-,092	**,448**	-,258
SPAIDD-M Item 13: Somatization	,034	-,263	,182	**-,501**
SPAIDD-M Item 14: Indecision	,061	**,483**	,185	-,224
SPAIDD-M Item 15: Avoidance	-,049	,083	,084	**-,512**
SPAIDD-M Item 16: Impaired abstractive thinking*	-,089	,020	**,710**	,122
SPAIDD-M Item 17: Impaired memory*	-,039	,075	**,632**	**,319**
SPAIDD-M Item 18: Affective flattening	,044	,291	**,427**	,000
SPAIDD-M Item 19: Retire at home	-,018	,198	,221	**-,562**
SPAIDD-M Item 20: Pica	,022	,243	-,140	,045
SPAIDD-M Item 21: Anxiety	,204	,157	-,137	**-,502**
SPAIDD-M Item 22: Reduced social interaction	-,028	**,771**	,030	-,008
SPAIDD-M Item 23: Apathy	,081	**,730**	,064	,149
SPAIDD-M Item 24: Irritability	**,596**	,173	-,060	-,249
SPAIDD-M Item 25: Weight loss	-,080	,031	**,307**	-,220
SPAIDD-M Item 26: Psychomotor agitation/restlessness	**,553**	,199	-,039	-,243
SPAIDD-M Item 27: Suicidality	,076	,283	,174	-,084
SPAIDD-M Item 28: Aggressiveness	**,601**	,155	-,076	-,198
SPAIDD-M Item 29: Affective lability	**,512**	-,013	,022	-,226
SPAIDD-M Item 30: Impaired judgment	**,452**	,103	,208	,065
SPAIDD-M Item 31: Substance abuse	**,307**	-,232	,190	-,169
SPAIDD-M Item 32: Distractibility	**,463**	,099	,284	,254
SPAIDD-M Item 33: Sexual activity alterations	**,622**	-,055	-,008	,095
SPAIDD-M Item 34: Euphoria	**,640**	,004	-,046	,166

SPAIDD-M Item 35: Purpose hyperactivity	**,653**	,001	,157	-,002
SPAIDD-M Item 36: Grandiosity	**,337**	-,251	**,391**	,072
SPAIDD-M Item 37: Pressured communication	**,677**	,024	,026	-,037
SPAIDD-M Item 38: Purposeless hyperactivity	**,512**	,366	,137	,259
SPAIDD-M Item 39: Reduced need for sleep	**,585**	,079	,020	,135
SPAIDD-M Item 40: Defiant/antisocial behavior	**,507**	,243	-,007	-,244
SPAIDD-M Item 41: Disorganization	,180	**,464**	**,397**	,065
SPAIDD-M Item 42: Manipulation/exploitation	**,508**	-,132	-,026	-,174
SPAIDD-M Item 43: Undiscriminating socialization	**,467**	-,274	,083	**,394**
SPAIDD-M Item 44: Catatonia	-,020	**,386**	,045	-,060
SPAIDD-M Item 45: Hallucinations	,073	,070	**,411**	-,177
SPAIDD-M Item 46: Delusion	,151	-,117	**,507**	-,207

3.3.5 Test-retest reliability

The stability and precision of the SPAIDD-M construct across time has been tested via the replication of five SPAIDD-M questionnaires, one per each ID level, after two-to-three months from the first completion. For all the five proofs, we found very good test-retest reliability as the Pearson's r and Kendall's τ-b value ranged from .77 to .96 with a p<.001.

3.3.6 Concurring validity

The concurring validity was tested comparing at first the SPAIDD-M diagnoses for MDD, BD I, BD II and BD otherwise specified with the respective DSM-5 diagnoses, as shown in **Table 9**. The concurrent validity was high for MDD, BD I and BD II diagnoses as demonstrated by both Pearson's r and Spearman's ρ coefficients >0.7, with p=<.001. The correlation resulted only moderate for BD otherwise specified.

Table 9. Correlations of the SPAIDD-M and DSM-5 diagnoses

Diagnosis	Coefficient*	Correlation value	p
MDD	r and ρ	.636	<.001
BD I	r and ρ	.929	<.001
BD II	r and ρ	.791	<.001
BD otherwise specified	r and ρ	.368	<.001

* Pearson's r and Spearman's ρ

A further correlation test was performed between the DASH-II subscales for depression and mania and the diagnoses of MDE and (hypo)manic episode. In this analysis, the correlation between the diagnosis of MDE and the DASH-II depression subscale was moderate (Pearson's r=.310 and Spearman's ρ=.474 p <.001), The correlation for the (hypo)manic episode and the DASH-II mania subscale was instead low according to the

Pearson correlation test (Pearson's r=.283, p<.001) and moderate using Spearman's test (Spearman's ρ=.480, p<.001).

3.4 Mood Disorders in intellectually disabled persons: associated socio-demographic, familial, medical and psychiatric comorbidity features

In our sample ID individuals with a clinical diagnosis of MD resulted younger than no-MD probands, even if the statistical significance was not reached (p=.074). No differences emerged between the MD and no-MD subjects regarding gender distribution and mean BMI. The χ^2 statistics relative to the recruitment source evidenced the homogeneity of the sample, as no significant differences were detected. However, it has to be noted that individuals with MD had been slightly more recruited from families, especially in ambulatory services, where the evaluation of psychiatric issues and behavioral disturbances is routinely executed (see **Table 10**).

Table 10. Significant demographic, familial, medical and psychiatric features: comparisons according to the clinical diagnosis of Mood Disorders

Features **N (%)**	**No-MD** **N=121**	**MD** **N=96**	**χ^2 or F**	**P**	**OR [95% CI]**
Demographic features					
Gender (M)	33 (15.2)	30 (31.3)	.41	NS	1.21 [.67-2.18]
Age, Mean (SD	41.96 (16.94)	39.76 (15.25)	13.22	NS (.074)	5.63 [1.86-16.99]
BMI, Mean (SD)	21.02 (8.16)	25.39 (11.35)	.02	NS	2.97 [.91-9.72]
Recruitment source					
Residential facilities	54 (44.6)	45 (46.9)	3.76	.	
Rehabilitative centers	47 (38.8)	27 (28.1)			
Families	20 (16.5)	24 (25.0)		NS	
Familial comorbidity					
Familial NDs*	14 (22.2)	20 (29.9)	.98	NS	1.49 [.68-3.29]
Familial psychiatric disorder*	26 (36.1)	38 (55.9)	5.52	.019	2.24 [1.14-4.42]
Familial DDs	8 (11.3)	15 (22.7)	3.22	NS (.073)	2.32 [.91-5.90]
Familial medical illness*	30 (54.5.)	34 (55.7)	.02	NS	1.05 [.50-2.18]
Medical comorbidity**	70 (66.7)	68 (76.4)	2.23	NS	1.62 [.86-3.06]
ID-related genetic syndrome	23 (27.4)	12 (16.2)	2.84	NS (.092)	.51 [.24-1.12]
Motor disability	33 (31.4)	15 (17.0)	5.30	.021	.45 [.22-.90]
Axis I psychiatric comorbidity°°	23 (39.7)	39 (62.9)	6.49	.011	2.58 [1.24-5.39]
OCD-related disorders	2 (3.4)	13 (20.3)	8.21	.004	7.27 [1.56-33.75]
SSDs	10 (16.7)	2 (3.1)	6.50	.011	1.16 [.03-.77]
Schizoaffective disorder	9 (15.0)	0 (0.0)	10.20	.001	
BED	1 (1.7)	6 (9.7)	3.45	NS (.063)	6.11 [.71-52.37]

ADHD	5 (8.3)	16 (23.5)	5.37	.021	3.39 [1.16-9-90]
ICDs	4 (6.9)	18 (28.1)	9.28	.002	5.28 [1.67-16.73]
ODD	2 (3.4)	14 (22.2)	9.28	.002	8.00 [1.73-36.96]
Substance-related disorder	0 (0.0)	5 (8.1)	4.88	.027	
Axis II psychiatric comorbidity	8 (13.6)	23 (36.5)	8.47	.004	3-67 [1.48-9.06]
Cluster C personality disorder	5 (8.5)	16 (26.2)	6.55	.010	3.84 [1.31-11.30]
Severity related variables					
Attempted suicide	1 (1.0)	7 (8.0)	5.42	.020	8.38 [1.01-69.56]
Hospitalizations	5 (5.2)	18 (21.4)	10.75	.001	5.02 [1.77-14.20]
Number of hospitalizations, Mean (SD)	.12 (.83)	.70 (1.82)	24.65	<.001	
Psychopharmacological treatments	51 (51.0)	81 (91.0)	35.79	<.001	9.73 [4.26-22.21]
SSRI antidepressants	6 (6.0)	27 (30.3)	19.35	<.001	6.82 [2.66-17.48]
Tricyclic antidepressants	3 (3.0)	6 (6.7)	1.45	NS	2.34 [.57-9.64]
Other antidepressants	3 (3.0)	15 (16.9)	10.49	.001	6.55 [1.83-23.48]
Anticonvulsants	31 (31.0)	60 (67.4)	25.01	<.001	4.61 [2.49-8.50]
Lithium	2 (2.0)	9 (10.1)	5.65	.017	5.51 [1.16-26.24]
FGA	8 (8.0)	35 (39.3)	26.29	<.001	7.45 [3.22-17.24]
SGA	24 (24.0)	63 (70.8)	41.49	<.001	7.67 [4.02-14.66]
BDZ	19 (19.0)	49 (55.1)	26.58	<.001	5.22 [2.72-10.02]
Psychiatric adverse effects of antidepressants°	2 (16.7)	17 (45.9)	3.27	NS (.070)	4.25 [.82-22.13]
Adverse effects of antipsychotics°	12 (48.0)	38 (57.6)	.67	NS	1.47 [.58-3.70]

* The comparisons relative to the familial occurrence of the following specific neurodevelopmental disorders, psychiatric disorders and medical illnesses are not reported as far as not significant differences were detected: ID, ASD, ADHD, specific learning disorders and epilepsy; BDs, SSDs, anxiety disorders, OCD-related disorders, Substance-related disorders, somatic symptom disorders, personality disorders, ICD; autoimmunity diseases, allergies, sensory impairments, diabetes, obesity, cardiovascular diseases, motoric disability.

** The comparisons relative to the following medical comorbidities are not reported as far as not significant differences were detected: epilepsy, allergies, gastrointestinal disturbances, obesity, cardiovascular diseases, respiratory diseases, sensory impairments.

° The comparisons relative to the specific psychiatric adverse effects of antidepressants (irritability, (hypo)manic switch, mood instability, resistance) and specific adverse effects of antipsychotics (affective flattening and depressed mood, akathisia, EPS, metabolic effects) are not reported as far as not significant differences were detected.

°°The analysis of Axis I comorbidity does not include NDs and MDs. The comparisons relative to the following psychiatric disorders are not reported as far as not significant differences were detected: anxiety disorders, panic disorder, GAD, schizophrenia, EDs, anorexia, bulimia, NDs, ASD, specific learning disorders, conduct disorder, cluster A and B personality disorders

MD diagnosis was significantly associated to the presence of family members with at least one comorbid psychiatric disorder (55.9% vs. 36.1%, χ^2= 5.52 p=.019), but no specific psychiatric disorder have been found as significantly more associated to MD comparing to no-MD probands; the rate of familial DDs was actually doubled in MD participants but not significant (see **Table 10**).

The only significantly different medical comorbidity in the two groups was the presence of motor disabilities, also including a certain number of patients with cerebral palsy: motor disabilities had higher rates in no-MD individuals of the sample. Even the presence of an ascertained genetic syndrome related to ID showed a similar, but not significant trend. It has to be noticed that, comparing to the overall numerosity of the sample, the total number of genetic syndromes is relatively lower and mostly represented by trisomy 21 that is well-known to have mild association with psychiatric vulnerability (see **Table 10**).

The classes of psychotropic medications were compared between the two groups: all but tricyclic antidepressants showed higher rates in the MD group. MD was associated to higher risk of adverse effects of antidepressants and antipsychotics, although the statistical significance was not achieved in both cases (near for antidepressants, p=.070) (see **Table 10**).

We found MD to be associated to significantly higher rates of comorbid Axis I psychiatric disorders (OR=2.58, p=.011): the specific disorders showing significant differential occurrence in MD subjects included OCD-related disorders (p=.004), ADHD (p=.021), impulse control disorders and specifically oppositional-defiant disorder (p=-002), substance-related disorders (p=.027) and binge eating disorder (p=.063). By the contrary, in the no-MD group higher rates of schizophrenia spectrum disorders were found (p=.001) and it was expected as the presence of some SSDs represent an exclusionary criterion for the diagnosis of MD. On the other hand, the two groups did not show significantly different rates of personality disorders, exception given for cluster C personality disorders, reporting higher rates in MDs. These results evidenced MDs to be associated to a greater burden of psychiatric illness (see **Table 10**). This was confirmed by the significantly higher rates of attempted suicides, hospitalizations and their higher mean number, but also the higher mean raw scores of almost all the DASH-II psychopathological dimensions, not only mania and depression (detailed in **Table 11**).

Table 11. Psychopathological burden associated to mood disorders: comparisons of DASH-II raw scores according to the clinical diagnosis

DASH-II psychopathological dimension, Mean (SD)	**No-MD N=121**	**MD N=96**	**F**	**p**
Anxiety	6.86 (8.16)	10.50 (10.63)	12.70	.010
Depression	9.31 (8.59)	23.90 (13.05)	16.11	<.001
Impulse Control	13.13 (12.37)	27.73 (17.08)	18.96	<.001
Stereotypies/Tics	7.36 (7.14)	12.55 (9.19)	8.29	<.001
Organic disturbances	6.52 (6.47)	14.77 (8.15)	7.53	<.001
Schizophrenia	3.60 (6.08)	5.63 (4.54)	.39	.015
PDD/Autism	9.10 (8.68)	15.14 (10.73)	8.15	<.001
Mania	6.95 (6.86)	16.64 (9.36)	17.98	<.001
Eating issues	1.65 (3.19)	3. 80 (4.66)	10.75	<.001
Self-injurious behaviors	1.15 (2.39)	3.06 (5.10)	26.81	.001
Elimination issues	.64 (2.24)	.83 (2.30)	1.00	NS
Sleep disturbances	1.01 (2.25)	4.22 (4.59)	45.76	<.001
Sexual disorders	.67 (1.99)	2.14 (3.68)	31.32	.001

3.5 Mood disorders: clinical and course features associated to low-functioning Autism Spectrum Disorder

Another interesting point to explore was the relationship between MDs and ASD in individuals with ID. Including the overall sample, we made comparisons of clinical diagnoses of MDs and associated clinical features, starting from the co-occurrence of ASD. The relative χ^2 statistics are shown in **Table 12**.

Table 12: Clinical and course features of clinically diagnosed mood disorders: comparisons on the basis of the co-occurrence of autism spectrum disorder

Diagnosis **N (%)**	**No-ASD** **N=150**	**ASD** **N=83**	**χ^2**	**p**	**OR [95% CI]**
MDs	48 (35.6)	48 (58.5)	10.92	.001	2.56 [1.46-4.49]
DDs	19 (14.0)	17 (20.7)	1.70	NS	1.61 [.78-3.31]
MDD	16 (10.7)	14 (16.9)	1.83	NS	1.70 [.78-3.68]
PDD	2 (1.5)	3 (3.7)	1.09	NS	2.54 [.42-15.56]
BDs	20 (22.2)	31 (37.8)	6.13	.013	2.13 [1.16-3.89]
BD I	15 (11.0)	19 (23.2)	5.73	.017	2.43 [1.16-5.11]
BD II	5 (3.7)	6 (7.3)	1.42	NS	2.07 [.61-7.01]
Cyclothymic Disorder	1 (0.7)	1 (1.2)	.13	NS	1.67 [.10-27.01]
BD otherwise specified	8 (5.9)	4 (4.9)	.10	NS	.82 [.24-2.82]
Clinical and course features					
MDE with mixed features	16 (10.7)	21 (25.3)	8.57	.003	2.84 [1.39-5.81]
MDE with catatonic features	0 (0.0)	11 (13.3)	20.87	<.001	
MDE with psychotic features	22 (14.7)	13 (15.7)	.04	NS	1.08 [.51-2.28]
MDE with seasonal pattern	12 (8.0)	22 (26.5)	14.69	<.001	4.15 [1.93-8.92]
Euphoric (hypo)mania	23 (15.3)	18 (21.7)	1.49	NS	1.53 [.77-3.04]
Dysphoric (hypo)mania	21 (14.0)	26 (31.3)	9.96	.002	2.80 [1.46-5.39]
(Hypo)mania with mixed features	18 (12.0)	25 (30.1)	11.70	.001	3.16 [1.60-6.24]
(Hypo)mania with catatonic features	0 (0.0)	3 (3.6)	5.49	.019	
(Hypo)mania with psychotic features	21 (14.0)	13 (15.7)	.12	NS	1.14 [.54-2.42]
(Hypo)mania with seasonal pattern	11 (7.3)	12 (14.5)	3.05)	NS (.081)	2.14 [.90-5.08]
Rapid cycling BD course	18 (12.0)	18 (21.7)	3.84	.050	2.03 [.99-4.16]
Affective flattening/depressed mood under AP treatment	5 (11.6)	18 (36.0)	7.38	.007	4.28 [1.43-12.80]

No-ASD: subjects without the diagnosis of autism spectrum disorder; ASD: subjects with the diagnosis of autism spectrum disorder; MDs: Mood Disorders; DDs: Depressive Disorders; MDD: Major Depressive Disorder; PDD: Persistent Depressive Disorder; BDs: Bipolar Disorders; BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; MDE: Major Depressive Episode; AP: antipsychotic.

Comparing to subjects without an ASD diagnosis (no-ASD), the ASD group showed significantly higher rates of overall MDs (OR=2.56, p=.001) and specifically of BDs (OR= 2.13, p=.013) and BD I (OR=2.43, p=.017). No differences emerged regarding all DDs and soft bipolar diagnoses.

The presentation of MDE in ASD individuals resulted more frequently associated to mixed and catatonic features, as well as to a seasonal pattern. The related statistics were significant. Similarly, the diagnosis of ASD was also associated to higher prevalence of the same features during the excitatory phases. Moreover, (hypo)mania was significantly more frequently characterized by dysphoria, while euphoria did not differ between ASD and no-ASD participants. Finally, ASD patients reported a doubled risk to show a rapid cycling course of bipolar illness.

No differences between the two groups were evidenced regarding the development of psychiatric adverse effects of antidepressants, whereas ASD individuals reported significantly higher rates of antipsychotic-induced affective flattening and depressed mood, but not akathisia, EPS and metabolic side effects.

3.6 Depressive and Bipolar Disorders: prevalence rates according to SPAIDD-M diagnosis and comparisons of different diagnostic definitions

SPAIDD-M resulted positive for the diagnosis of a MD in 110 participants (47.2%), 59 (25.3%) had a DD and 70 (30.0%) had a BD. The comparisons of the rates in the three ID subgroups did not reveal significant differences. **Table 13** summarizes the χ^2 statistics for the three ID subgroups of all the DDs and BDs-related diagnoses. The three subgroups showed no statistically significant difference in the rate for all the DD and BD-related SPAIDD-M diagnoses.

Table 13. Depressive and Bipolar Disorders: comparisons of SPAIDD-M rates according to ID levels

Diagnoses N (%)	BIF/Mild ID N=66	Moderate ID N=88	Severe/Profound ID N=79	χ^2	p
Overall Mood Disorders	28 (42.4)	46 (52.3)	36 (45.6)	1.60	NS
Depressive Disorders	12 (18.2)	25 (28.4)	22 (27.8)	2.49	NS
MDD	10 (15.2)	21 (23.9)	16 (20.3)	1.78	NS
PDD	3 (4.5)	6 (6.8)	5 (6.3)	.37	NS
Dysphoric Premenstrual Disorder	0 (0.0)	0 (0.0)	0 (0.0)		
DD due to GMC or drugs	2 (3.1)	1 (1.1)	1 (1.3)	.97	NS
Bipolar Disorders	20 (30.3)	27 (30.7)	23 (29.1)	.05	NS
BD I	13 (19.7)	12 (13.6)	9 (11.4)	2.09	NS
BD II	2 (3.0)	6 (6.8)	3 (3.8)	1.43	NS
Cyclothymic Disorder	1 (1.5)	1 (1.1)	0 (0.0)	1.10	NS
BD otherwise specified	2 (3.0)	5 (5.7)	7 (8.9)	2.19	NS
BD due to GMC or drugs	1 (1.5)	1 (1.1)	0 (0.0)	1.10	NS

MDD: Major Depressive Disorder; PDD: Persistent Depressive Disorder; BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; GMC: General Medical Condition

Scheffè test performed for all the comparisons did not evidence statistically significant differences.

141 patients completed the full study protocol and the diagnoses of DDs and BDs were made according to different definitions, namely via the application of DSM-5 criteria for MDD, BD I, BD II and BD otherwise specified, the SPAIDD-M evaluation and a clinical expert diagnosis integrating all the anamnestic, observational and assessment information. **Table 14** summarizes the χ^2 statistics for all MD diagnoses according to three ID levels.

Table 14. Depressive and Bipolar Disorders: diagnoses according to different definitions and ID levels

Diagnoses N (%)		BIF/Mild ID N=47	Moderate ID N=46	Severe/Profound ID N=48	χ^2	p
MDD	DSM-5	5 (10.6)	12 (26.1)	9 (18.8)	3.69	NS
	SPAIDD-M	8 (17.0)	16 (34.8)	9 (18.8)	4.97	NS (.083)
	Clinical	6 (12.8)	8 (17.4)	9 (18.8)	.68	NS
PDD	SPAIDD-M	3 (6.4)	2 (4.3)	0 (0.0)	2.96	NS
	Clinical	0 (0.0)	1 (2.2)	0 (0.0)	2.08	NS
DD GMC and drug-related	SPAIDD-M	0 (0.0)	1 (2.2)	1 (2.1)	1.00	NS
	Clinical	0 (0.0)	1 (2.5)	1 (2.9)	1.05	NS
BD I	DSM-5	10 (21.3)	9 (19.6)	6 (12.5)	1.41	NS
	SPAIDD-M	11 (23.4)	9 (19.6)	6 (12.5)	1.94	NS
	Clinical	10 (21.3)	8 (17.4)	6 (12.5)	1.30	NS
BD II	DSM-5	2 (4.3)	3 (6.5)	2 (4.2)	.35	NS
	SPAIDD-M	2 (4.3)	4 (8.7)	2 (4.2)	1.17	NS
	Clinical	2 (4.3)	4 (8.7)	2 (4.2)	1.17	NS
Cyclothymic Disorder	SPAIDD-M	1 (2.1)	0 (0.0)	0 (0.0)	2.01	NS
	Clinical	1 (2.1)	0 (0.0)	0 (0.0)	2.01	NS
BD otherwise Specified	DSM-5	5 (10.6)	2 (4.3)	0 (0.0)	5.75	NS (.056)
	SPAIDD-M	2 (4.3)	2 (4.3)	4 (8.3)	.96	NS
	Clinical	1 (2.1)	3 (6.5)	2 (4.2)	1.10	NS
BD GMC or drug-related	SPAIDD-M	1 (2.2)	1 (2.2)	0 (0.0)	1.04	NS
	Clinical	1 (2.6)	1 (2.5)	0 (0.0)	.63	NS

MDD: Major Depressive Disorder; PDD: Persistent Depressive Disorder; DD: Depressive Disorders; BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; GMC: General Medical Condition
Scheffè test performed for all the comparisons did not evidence statistically significant differences.

For all the diagnoses, it can be identified a diagnostic trend indicating higher rates per diagnosis obtained with the SPAIDD-M assessment comparing to the application of adapted DSM-5 criteria and the final clinical diagnosis. This effect seemed to be more pronounced for DDs than BD ones. For example, the prevalence rate of MDD in moderate ID subjects resulted 26.1% and 34.8% according to DSM.5 criteria and SPAIDD-M respectively, whereas the clinical judgement evidenced a prevalence rate 17.4%. It is possible that the high load of antipsychotic treatments and their psychiatric side effects as well as the high prevalence of SSDs in the sample might have influenced the evaluation, especially reducing the specificity of SPAIDD-M results.

Table 15. Demographic and socio-economic features in individuals with intellectual disability and co-occurring mood disorders: comparisons between Depressive and Bipolar Disorders according to SPAIDD-M definition

Demographic and socio-economic features	Depressive Disorders N=47	Bipolar Disorders N=63	χ^2 or F	p	OR [95% CI]
Gender (M) N (%)	36 (76.6)	44 (69.8)	.62	NS	
Age, Mean (sd)	41.94 (15.10)	37.49 (14.95)	.02	NS	
BMI, Mean (sd)	23.77 (5.03)	27.39 (12.74)	3.1	NS (.082)	
ID levels N (%)					
Mild	10 (21.3)	18 (28.6)			
Moderate	21 (44.7)	25 (39.7)			
Severe	16 (34.0)	20 (31.7)	.77	NS	
Recruitment source N (%)					
Residential facilities	26 (55.3)	27 (42.9)			
Rehabilitative centers	9 (19.1)	23 (36.5)			
Families	12 (25.5)	13 (20.6)	3.94	NS	
Adopted N (%)	1 (2.4)	3 (5.8)	.62	NS	2.45 [.25-24.46]
Invalidity pension N (%)	39 (97.5)	49 (94.2)	.58	NS	.42 [.04-4.19]
Employed N (%)	2 (4.9)	7 (13.5)	1.93	NS	3.03 [.60-15.47]
Problems with justice N (%)	1 (2.6)	1 (2.0)	.27	NS	.79 [.05-13.08]
Provenance N (%)					
Urban, big city	20 (48.8)	14 (28.0)			
Periphery, small city	16 (39.0)	31 (62.0)			
Rural	5 (12.2)	5 (10.0)	5.01	NS	
Familial economic level N (%)					
Low income	8 (21.6)	9 (18.4)			
Medium income	25 (67.6)	29 (59.2)			
High income	4 (10.8)	11 (22.4)	1.99	NS	
Educational Level N (%)					
None	8 (20.5)	3 (6.8)			
Primary	2 (5.1)	4 (9.1)			
Secondary	19 (48.7)	24 (54.5)			
Tertiary	29 (23.1)	13 (29.5)	4.97	NS	
Educational support	30 (78.4)	37 (84.1)	.36	NS	1.41 [.46-4.33]
Quality of familial relationships N (%)					
Low	11 (29.7)	16 (34.0)			
Medium	18 (48.6)	18 (38.3)			
High	8 (21.6)	13 (27.7)	.94	NS	
Friendships N (%)					
None	20 (51.3)	19 (38.8)			
Few	17 (43.6)	25 (51.0)			
Normal	2 (5.1)	5 (10.2)	1.72	NS	

3.7 Socio-demographic and clinical differences between Depressive and Bipolar patients with Intellectual Disability

The dependent variable used for the analyses was the diagnosis of DDs and BDs according to the SPAIDD-M definition. The participants included in these analyses were 110.

No differences emerged regarding gender and mean age of depressive and bipolar ID patients, whereas the mean BMI was slightly different in the two groups, although not achieving the statistical significance (χ^2=3.1, p=.082). None of the other socio-demographic variables explored differentiated between the two diagnoses. The results are detailed in **Table 15**.

The χ^2 tests concerning pregnancy and delivery showed that BDs patients with ID more frequently than DDs patients use medications during pregnancy and its course with the presentation of a variety of problematic issues (for example miscarriage risk, placenta previa etc.) (χ^2=4.10, p=.043; χ^2=4.77, p=.029, respectively).

The comparisons of the physiological parameters after birth and achievement of developmental milestones did not differ between the two groups rather for the delay of the development of autonomous locomotion, more prevalent in the DDs group. All the χ^2 tests are detailed in **Table 16**.

No medical illness but obesity showed statistically significant differences in DDs and BDs probands, including the prevalence of ID-related genetic syndromes as well as immunity dysreactive disorders. BDs individuals had significantly higher prevalence of obesity, with an OR=4.50 (χ^2=7.05, p=.008). **Table 16** summarizes also the comparisons regarding medical and familial features associated to DDs and BDs diagnoses.

The familial co-occurrence of neuropsychiatric and psychiatric conditions among family member of the probands was also explored. DDs subjects showed a prevalence rate of familial ASD of 9.1% comparing to none of BDs participants. By the contrary, comparing to DDs, BDs subjects showed significantly higher rates for overall familial psychiatric comorbidity (OR=2.68, χ^2=4.24, p=.039), and specifically a higher familial load for BD and personality disorders (32.6% vs. 3.3%, OR=14.00 in both cases). BD was also associated to slightly higher prevalence rates of familial psychotic and eating disorders but not reaching the statistical significance.

Table 16. Physiological, medical and familial features in individuals with intellectual disability and co-occurring mood disorders: comparisons between Depressive and Bipolar Disorders according to SPAIDD-M definition

Physiological features N (%)	**Depressive Disorders N=47**	**Bipolar Disorders N=63**	**χ^2**	**p**	**OR [95% CI]**
Pregnancy					
Use of medications	1 (3.7)	6 (22.2)	4.10	.043	7.43 [.83-66.62]
Problematic course	3 (9.7)	10 (32.3)	4.77	.029	4.44 [1.09-18-18]
At term	25 (86.2)	24 (77.4)			
Preterm	2 (6.9)	4 (12.9)			
Post-term	2 (6.9)	3 (9.7)	.82	NS	
Delivery					
Eutocic	19 (61.3)	15 (50.0)			

Dystocic	9 (29.0)	9 (30.0)			
Planned caesarean section	0 (0.0)	3 (10.0)			
Urgency caesarean section	3 (9.7)	3 (10.0)	3.46	NS	
Physiological developmental variables N (%)*					
Delayed locomotion	22 (68.8)	16 (43.2)	4.51	.034	.35 [.13-.93]
Medical comorbidity N (%)					
Genetic syndrome related to ID	5 (12.8)	7 (15.9)	.16	NS	1.29 [.37-4.44]
Overall medical comorbidities	34 (81)	40 (69.0)	1.82	NS	.52 [.20-1.35]
Epilepsy	12 (28.6)	10 (17.5)	1.70	NS	.53 [.20-1.38]
Gastrointestinal disturbances	9 (21.4)	8 (14.0)	.93	NS	.60 [.21-1.71]
Diabetes	1 (2.4)	3 (5.3)	.52	NS	2.28 [.23-22.70]
Obesity	4 (9.5)	18 (32.1)	7.05	.008	4.50 [1.39-14.54]
Cardiovascular disorders	4 (9.8)	4 (7.0)	.24	NS	.70 [.16-2-97]
Immunity dysreactivity**	9 (23.1)	14 (29.2)	.41	NS	1.37 [.52-3.52]
Motoric disability	6 (14.3)	8 (14.0)	.001	NS	.98 [.31-3.07]
Sensory impairments	2 (4.8)	5 (8.8)	.59	NS	1.92 [.36-10.43]
Familial history N (%)					
Familial history for neuropsychiatric disorders	10 (30.3)	12 (27.9)	.05	NS	.89 [.33-2.41]
Familial ASD	3 (9.1)	0 (0.0)	3.98	.046	
Familial ID	7 (21.2)	9 (21.4)	.001	NS	1.01 [.33-3.08]
Familial history for medical illness	14 (46.7)	24 (61.5)	1.52	NS	1.83 [.70-4.80]
Familial autoimmune diseases	2 (6.7)	6 (15.4)	1.26	NS	2.55 [.48-13.63]
Familial history for psychiatric disorders* **	13 (41.9)	29 (65.9)	4.24	.039	2.68 [1.04-6.90]
Familial DDs	4 (13.3)	11 (58.4)	1.62	NS	2.23 [.64-7.85]
Familial BDs	1 (3.3)	14 (32.6)	9.25	.002	14.00 [1.73-113.53]
Familial Psychotic Disorders	2 (6.7)	9 (20.9)	2.81	NS (.094)	3.71 [.74-18.57]
Familial Personality Disorders	1 (3.3)	14 (32.6)	9.25	.002	14.00 [1.73-113.53]
Familial ED	2 6.7)	0 (0.0)	2.95	NS (.086)	

*First physiological acts, breast feeding, psychomotor milestones achievement, and delay of the language development not reported as far as not significant differences were detected.
** Immunity dysreactivity includes autoimmunity diseases and allergies.
*** The comparisons relative to the following psychiatric disorders in first-degree family members are not reported as far as not significant differences were detected: Anxiety disorders, Obsessive-Compulsive and related disorders, Trauma and stress-related disorders, Addiction-related disorders, Somatic Symptom and related disorders, Impulse Control disorders.
ASD: Autism Spectrum Disorder; ID: Intellectual Disability; DDs: Depressive Disorders; BDs: Bipolar Disorders.

Table 17 shows the comparisons of psychiatric comorbidity according to the clinical evaluation made during the present study. The clinical diagnosis of DDs was confirmed in the 68.2% of the subjects resulted positive to DDs at the SPAIDD-M evaluation, whereas the 3.2% of the SPAIDD-M/BDs patients received a final diagnosis of DDs, namely an MDD diagnosis. By the contrary, the 11.4% of the patients with a SPAIDD-M diagnosis of DDs, were reframed as clinically bipolar: the 6.8% as BD I, the 9.1% as BDII and the 2.3% as BD otherwise specified.

Table 17. Clinically diagnosed psychiatric comorbidity in individuals with intellectual disability and co-occurring mood disorders: comparisons between Depressive and Bipolar Disorders according to SPAIDD-M definition

Psychiatric comorbidity N (%)	Depressive Disorders N=47	Bipolar Disorders N=63	χ^2	p	OR [95% CI]*
DDs	30 (68.2)	2 (3.2)	51.52	<.001	.02 [.00-.07]
MDD	28 (59.6)	2 (3.2)	43.17	<.001	.02 [.01-10]
PDD	5 (11.4)	0 (0.0)	7.39	.007	
BDs	5 (11.4)	55 (88.7)	62.68	<.001	61.29 [18.12-207.33]
BD I	3 (6.8)	31 (50.0)	22.03	<.001	13.67 [3.82-48.84]
BD II	1 (9.1)	10 (16.1)	5.31	.021	8.27 [1.02-67.19]
Cyclothymic Disorder	0 (0.0)	2 (3.2)	1.45	NS	
BD otherwise specified	1 (2.3)	11 (17.7)	6.13	.013	9.28 [1.15-74.76]
Neurodevelopmental disord.	17 (51.5)	32 (64.3)	1.28	NS	1.67 [.68-4.09]
ASD	16 (48.5)	28 (56.0)	.45	NS	1.35 [.56-3.27]
ADHD	2 (7.1)	16 (32.7)	6.47	.011	6.30 [1.33-29.91]
Anxiety Disorders	9 (37.5)	9 (18.8)	3.00	NS (.083)	.39 [.13-1.16]
Panic disorder	3 (6.4)	3 (4.8)	.14	NS	.73 [.14-3.81]
GAD	6 (25.0)	2 (4.3)	6.84	.009	.13 [.03-.72]
OCD-related disorders	2 (8.3)	11 (22.4)	2.19	NS	3.18 [.65-15.70]
SSDs	8 (29.6)	3 (6.3)	7.55	.006	.16 [.04-.66]
Schizophrenia	1 (3.79	0 (0.0)	1.77	NS	
Schizoaffective disorder	7 (25.9)	2 (4.3)	7.54	.006	.13 [.02-.67]
EDs	0 (0.0)	8 (17.0)	4.60	.032	
Anorexia	0 (0.0)	2 (4.3)	1.05	NS	
Bulimia	0 (0.0)	1 (2.1)	.52	NS	
BED	0 (0.0)	7 (14.9)	3.97	.046	
ICDs	2 (8.0)	16 (33.3)	5.60	.017	5.75 [1.20-27.49]
ODD	2 (8.0)	12 (25.5)	3.20	NS (.074)	3.94 [.81-19.27]
Conduct disorders	1 (4.0)	0 (0.0)	1.91	NS	
Substance-related disorders	0 (0.0)	4 (8.5)	2.16	NS	
Personality disorders	5 (20.8)	23 (47.9)	4.94	.026	3.50 [1.12-10.89]
Cluster A PDs	3 (12.5)	5 (10.6)	.06	NS	.83 [.18-3.83]
Cluster B PDs	1 (4.2)	7 (14.9)	1.83	NS	4.03 [.47-34.80]
Cluster C PDs	4 (17.4)	15 (31.9)	1.65	NS	2.23 [.64-7.70]

*The dependent variable was the diagnosis of BD according to SPAIDD-M.
DDs: Depressive Disorders; BDs: Bipolar Disorders; MDD: Major Depressive Disorder; PDD: Persistent Depressive Disorder; BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; GAD: Generalized Anxiety Disorder; OCD: Obsessive-Compulsive Disorder; SSDs: Schizophrenia Spectrum Disorders; Eds: Eating Disorders; BED: Binge Eating Disorder; ICDs: Impulse Control Disorders; ODD: Oppositional-Defiant Disorder; PDs: Personality Disorders

The SPADD-M DDs and BDs diagnoses were not significantly associated to different clinical diagnoses of most neurodevelopmental and psychiatric disorders with some exceptions. ADHD was more common in the BDs group (32.7% vs. 7.1%, χ^2=6.47, p=.011), as well as BED (14.9% vs. 0.0%, χ^2=3.97, p=.046), overall personality disorders (47.9% vs. 20.8%, χ^2=4.94, p=.026), and impulse control disorders (33.3% vs. 8.0%, χ^2=5.60, p=.017). Among the impulse control disorders, no differences were evidenced, but the prevalence rate of oppositional-defiant disorder was slightly higher in bipolar than depressive patients (25.5% vs. 8.0%). Anxiety disorders resulted more prevalent in DDs individuals, especially GAD (25.0% vs. 4.3%, χ^2=6.84, p=.009). SSD clinical diagnoses showed significantly higher rates among DDs subjects (29.6% vs. 6.3%, χ^2=7.55, p=.006), supporting the hypothesis that a significant proportion of probands resulted positive for DDs at the SPAIDD-M evaluation showed large clinical overlap with SSDs, mostly with schizoaffective disorder depressive subtype. This effect could be far less extended for SPAIDD-M bipolar diagnoses.

Two multiple logistic regression analyses were performed to identify the significant variables independently associated to the SPAIDD-M diagnosis of BD and those variables associated to the clinical diagnosis of BD. The results are reported in **Tables 18** and **19**, respectively.

Table 18. Multiple Logistic Regression backward procedure of familial and psychiatric comorbidity features on SPAIDD-M BD diagnosis in 110 persons with ID and MD.

Variables	F	Wald	p	OR [95% CI]
Familial comorbidity for psychiatric disorders	3.12	6.864	.009	22.71 [2.20-234.81]
GAD	- 2.10	3.0162	.075	.12 [.01-1.24]
BED	21.83	.000	.999	
ADHD	2.87	5.32	.021	17.57 [1.54-200.95]

Wald=5.863, df 1 p=.015

Variables not in equation: Familial comorbidity for ASD, bipolar disorders and personality disorders, clinical diagnosis of SSDs, impulse control disorders and personality disorders

The first regression model, applied with backward procedure, found the presence of psychiatric comorbidity in family members together with the co-occurrence of BD and ADHD, independently predictive of the positivity SPAIDD-M diagnosis for BD. On the other hand, the co-occurrence of GAD seemed not to predict the belonging to the BDS group but to DDs. Specific disorders in family members, namely ASD, BD and personality disorders, as well as the diagnosis of co-occurring psychotic spectrum, impulse control and personality disorders were excluded from the regression model.

The multiple logistic regression model relative to the clinical diagnosis of BDs in the subsample of probands with a MDs diagnosis, gave similar results. However, it was found that the presence of ASD in family members was significantly not predictive to belong to the BD group, whereas BED was excluded by the model (see **Table 19**).

Table 19. Multiple Logistic Regression backward procedure of familial and psychiatric comorbidity features on clinical BD diagnosis in 96 persons with ID and MD.

Variables	T	Wald	p	OR [95% CI]
Familial comorbidity for psychiatric disorders	3.44	1.22	.005	31.04 [2.86-336.88]
Familial comorbidity for ASD	-23.95	.000	1.000	.000
GAD	- 3.14	4.681	.030	.04 [.00-.74]
ADHD	1.62	2.46	.117	5.05 [.67-38.17]

Wald=6.609, df 1 p=.010

Variables not in equation: Familial comorbidity for bipolar disorders and personality disorders, clinical diagnosis of SSDs, impulse control disorders, BED, and personality disorders

As shown in **Table 20**, DDs an BDs SPAIDD-M diagnoses were associated to similar rates and mean number of psychiatric hospitalizations, as well as similar rates of suicide attempts. The rates of hospitalizations, around 25%, were relatively low considering the high prevalence of BD type I and the severe burden of medical and psychiatric comorbidity. The use of psychotropic medication was comparable between the two groups too, overcoming in both cases the 90%. No differences were identified relatively to the use of all antidepressant classes, also if the use of SSRIs was about one third lower in BD patients. By the contrary, the diagnosis of BDs was associated to higher rates of the use of TCAs (p=.028), mostly trimipramine, and other antidepressants (p=.079), mostly NASSAs, for the treatment of co-occurring anxiety symptoms. As expected, the use of lithium salts was far more associated to BDs diagnosis (OR=6.86), even if the rate was only the 14.0%. The diagnosis of BDs was also associated to a significantly larger use of antipsychotics, both FGAs (OR=3.26, p=.071), SGAs (OR=8.45, p=.004), benzodiazepines (OR=3.11, p=.078) and other sedative medications (OR=15.00, p=.001).

Among the 39 patients past or currently taking antidepressants (39.0% of SPAIDD-M MDs diagnosed subjects), 18 had experienced the psychiatric adverse effects of antidepressants. The rates of these adverse effects resulted higher in the BDs group but the statistical significance was not achieved (54.4% vs. 37.5%). Considering the specific adverse effects, the χ^2 statistics did not identify significant differences in the prevalence of antidepressant-induced irritability and activation symptoms, nor resistance to antidepressants. The SPAIDD-M BDs diagnosis was associated to significantly higher rates of (hypo)manic switch under antidepressant treatment (χ^2=4.19, p=.041). The induction of mood instability was more frequent in BDs than in DDs subjects but it was only near to the statistical significance.

The 80% of MDs subjects diagnosed via SPAIDD-M, reported antipsychotics side effects, but no differences were identified between DDs and BDs. Antipsychotic-induced akathisia was reported only in BDs patients (χ^2=5.50, p=.019).

Table 20. Psychopharmacological treatments and indirect severity indices in individuals with intellectual disability and co-occurring mood disorders: comparisons between Depressive and Bipolar Disorders according to SPAIDD-M definition

Clinical features N (%)	**Depressive Disorders N=47**	**Bipolar Disorders N=63**	**χ^2 or F**	**p**	**OR [95% CI]**
Psychiatric hospitalizations	11 (26.2)	12 (23.5)	.08	NS	.87 [.34-2.23]
Number of psychiatric hospitalizations, Mean (SD)	.74 (1.78)	.90 (2.18)	.60	NS	
Suicide attempts	3 (7.0)	4 (7.3)	.003	NS	1.05 [.22-4.94]
Psychopharmacological treatments	40 (93.0)	52 (91.2)	.11	NS	.78 [.18-3.46]
SSRIs	15 (34.9)	13 (22.8)	1.77	NS	.55 [.23-1.33]
TCAs	0 (0.0)	6 (10.5)	4.82	.028	
Other antidepressants	3 (7.0)	11 (19.3)	3.09	NS (.079)	3.19 [.83-12.24]
Anticonvulsants	27 (62.8)	41 (71.9)	.94	NS	1.52 [.65-3.54]
Lithium	1 (2.3)	8 (14.0)	4.10	.043	6.86 [.82-57.09]
FGAs	12 (27.9)	26 (45.6)	3.26	NS (.071)	2.17 [.93-5.05]
SGAs	25 (58.1)	48 (84.2)	8.45	.004	3.84 [1.51-9.78]
BDZ	18 (41.9)	34 (59.6)	3.11	NS (.078)	2.05 [.92-4.59]
Other sedatives	1 (2.3)	15 (26.3)	10.50	.001	15.00 [1.90-118.75]
Psychiatric adverse effects with antidepressants	6 (37.5)	12 (54.5)	1.08	NS	2.00 [.54-7.45]
Irritability AD	3 (18.8)	10 (45.5)	2.94	NS (.087)	3.61 [.80-16.35]
(Hypo)manic switch	0 (0.0)	5 (22.7)	4.19	.041	
Mood instability AD	2 (12.5)	5 (22.7)	.65	NS	2.06 [.35-12.28]
Resistance to AD	1 (6.3)	0 (0.0)	1.41	NS	
Adverse effects with antipsychotics	15 (55.6)	32 (64.0)	.53	NS	1.42 [.55-3.69]
AP affective flattening/depressed mood	5 (18.5)	17 (34.0)	2.06	NS	2.27 [.73-7.04]
AP akathisia	0 (0.0)	9 (18.0)	5.50	.019	
AP EPS	8 (29.6)	17 (34.0)	.15	NS	1.22 [.45-3.37]
AP metabolic effects/weight gain	8 (29.6)	19 (38.0)	.54	NS	1.46 [.55-3.97]

SSRIs: Selective Serotonin Reuptake inhibitors; TCA: Tricyclic Antidepressants; FGA: First Generation Antipsychotics; SGA: Second Generation Antipsychotics; BDZ: Benzodiazepines; AD: antidepressants; AP: Antipsychotics; EPS: extrapyramidal effects

3.8 Clinical and course features of Major Depressive Episodes and Depressive Disorders in persons with ID.

As shown in **Table 21**, the χ^2 statistics comparing DDs and BDs in regards to the specifiers for the MDE, including the MDE related to a general medical condition or the assumptions of substances and medications, the presence during the episode of catatonic, psychotic and mixed features, and the seasonal pattern of depressive episodes, did not reveal any statistical difference, with the exception of the former specifier (episode CMG or drug-related), and plus, none of the DDs patients had reported this condition. This difference was not confirmed repeating the statistics considering the final clinical diagnoses of DDs and BDs (MDE GMC/drug related: 8.6% in DDs vs. 8.2% in BDs, χ^2=.004, ns).

As already noted, the high prevalence of psychotic symptoms in the SPAIDD-M DDs group might be related to the high prevalence of depressive syndromic pictures in patients clinically reframed as belonging the SSDs category. However, although with a consistent reshaping of the rate, the two groups of MDs did not differ for the presence of psychosis during MDE even considering the final clinical diagnoses (MDE with psychotic features: 20.0% in DDs vs. 27.7% in BDs, χ^2=.73, ns).

Table 21. Clinical features of major depressive episode in individuals with intellectual disability and co-occurring mood disorders: comparisons between Depressive and Bipolar Disorders according to SPAIDD-M definition

Clinical features N (%)	Depressive Disorders N=47	Bipolar Disorders N=63	χ^2	P	OR [95% CI]
GMC/drug-related MDE	0 (0.0)	5 (7.9)	3.91	.048	.55 [.47-.66]
Catatonic features	4 (8.5)	6 (9.5)	.03	NS	1.13 [.30-1.26]
Psychotic features	16 (34.0)	17 (27.0)	.64	NS	.72 [.32-1.63]
Seasonal pattern	9 (19.1)	20 (31.7)	2.20	NS	1.96 [.80-4.83]
Mixed features	17 (36.2)	19 (30.2)	.44	NS	.76 [.34-1.70]

To the best of our knowledge, this is the first study accounting for mixed features of affective episodes in intellectually disabled persons. The prevalence of MDE with mixed features in the overall sample was 21.7%. Noteworthy, we included in these analyses only those participants in which the completion of the relative SPAIDD-M section had been verified by the CREA team to improve the clinical validity. Unexpectedly, we did not find significant differences between DDs and BDs in the prevalence rates of mixed features during MDE, according to both the SPAIDD-M and the clinical diagnoses. Although not significant, we found that the rate of mixed depressive features was higher in DDs than in BDs patients, reaching a rate of 50%. The comparisons regarding individual, non-overlapping, excitatory symptoms during MDE did non evidence

significant differences between the two diagnostic groups. The relative total score means for mixed symptoms were comparable in DDs and BDs ID probands. The results are summarized in **Table 22**.

Table 22: Mixed features during MDE: comparisons between Depressive and Bipolar Disorders according to SPAIDD-M definition

Clinical features N (%)		**Depressive Disorders N=29**	**Bipolar Disorders N=54**	**χ^2**	**p**	**OR [95% CI]**
Mixed features	**SPAIDD-M**	14 (48.3)	16 (29.6)	2.84	NS (.092)	.45 [.18-1.15]
	Clinical	11 (50.0)	14 (28.6)	3.06	NS (.080)	.40 [.14-1.13]
Non-overlapping SPAIDD-M behavioral equivalents of manic symptoms during MDE						
Euphoria		2 (6.9)	4 (7.4)	.007	NS	1.08 [.19-6.28]
Increased energy		1 (3.4)	2 (3.7)	.004	NS	1.08 [.09-12.41]
Grandiosity		3 (10.3)	2 (3.7)	1.47	NS	.33 [.05-2.12]
Pressured communication		6 (20.7)	16 (29.6)	.77	NS	1.61 [.55-4.7]
Purposeless hyperactivity		5 (17.2)	15 (27.8)	1.15	NS	1.85 [.60-5.73]
Reduced need for sleep		2 (6.9)	3 (5.6)	.06	NS	.79 [.13-5.05]
Defiant/antisocial behavior		21 (72.4)	31 (57.4)	1.82	NS	.51 [.19-1.36]
Disorganization		12 (41.4)	13 (24.1)	2.68	NS	.45 [.17-1.18]
Manipulation/exploitation		11 (37.9)	16 (29.6)	.59	NS	.69 [.27-1.78]
Hyper-social behavior		3 (10.3)	6 (11.1)	1.08	NS	1.08 [.25-4.69]
Relative total score (hypo)manic features during MDE, Mean (SD)		.23 (.15)	.20 (.19)	2.10	NS	

MDE: Major Depressive Episode

3.9 Clinical and course features of (hypo)manic episodes and Bipolar Disorders in persons with ID.

Among the 70 participants with a SPAIDD-M test positive for a bipolar spectrum disorder, two had experienced (hypo)manic episodes only related to a general medical condition, medications or drugs (2.9%). Catatonic features resulted lower than expected, as they were reported during (hypo)mania only in one patient (1.4%). A seasonal pattern of the excitatory syndromic picture had been identified in the 21.4% of the sample. Psychotic and mixed features during the excitatory phases characterized the 27.1% and 44.3% of the bipolar ID patients, respectively. The 22.9% of the BDs sample had a rapid cycling course.

A clinical diagnosis of BD was confirmed in 61 probands. The frequencies of the above mentioned descriptive clinical features resulted similar: the CMG/drug related episode was reported in the 3.3%, catatonic features in the 1.6%, a seasonal pattern characterized the 23.0% of the sample. Manic episodes with psychotic features

were reported in the 29.5% of the cases, whereas (hypo)mania with mixed features had been experienced by the 21.7% of the sample. The rates of rapid cycling increased to about 30% in BD clinically diagnosed patients. **Table 23** summarizes the comparisons regarding clinical and course features of the affective illness in different types of BD. Soft bipolar diagnoses included BD II and BD otherwise specified. The two groups showed similar distributions of gender, age and BMI scores. The presence of psychotic features emerged as significantly different between the two groups, not only during the excitatory phases (by definition), but also during the depressive ones (47.1% vs. 2.8%). BD type I was also associated to higher rates of dysphoria, characterizing the (hypo)manic episodes almost invariably (97.1%), and higher rates of seasonal pattern for the depressive phases (41.2% vs. 22.2%). No differences were detected regarding the prevalence rates of MDE with mixed features, while (hypo)mania with mixed features was more prevalent in soft BDs (30.6% in BD I vs. 58.8% in soft BDs). The results were all replicated using the clinical diagnoses of BD instead of SPAIDD-M diagnoses.

Table 23. Clinical features and course of Bipolar Disorders in individuals with intellectual disability: comparisons between Bipolar Disorder type I and soft bipolar spectrum disorders according to SPAIDD-M definition*

Clinical features	**BD I N=36**	**Soft BD N=34**	**χ^2 or F**	**p**	**OR [95% CI]**
Age, Mean (SD)	36.47 (15.02)	40.64 (15.07)	.002	NS	
Gender, M	10 (29.4)	10 (27.8)	.02	NS	1.08 [.38-3.06]
BMI, Mean (SD)	26.41 (6.07)	27.22 (15.97)	.93	NS	
Clinical features of (hypo)manic episode N (%)					
GMC/drug-related (hypo)manic episode	0 (0.0)	2 (5.6)	1.94	NS	
Catatonic features	1 (2.9)	0 (0.0)	1.07	NS	
Psychotic features	19 (55.9)	0 (0.0)	27.61	<.001	
Seasonal pattern	9 (26.5)	6 (16.7)	1.00	NS	1.80 [.56-5.75]
Rapid cycling	10 (29.4)	6 (16.7)	1.61	NS	2.08 [.66-6.55]
Mixed features	11 (30.6)	20 (58.8)	5.66	.017	3.25 [1.21-8.70]
Euphoric (hypo)mania	23 (67.6)	18 (50.0)	2.24	NS	2.09 [.79-5.52]
Dysphoric (hypo)mania	33 (97.1)	13 (36.1)	28.83	<.001	58.39 [7.13-477.96]
Clinical features of MDE N (%)					
GMC/drug-related MDE	3 (8.8)	2 (51.4)	.28	NS	1.65 [.26-10.51]
Catatonic features	4 (11.8)	2 (5.6)	.86	NS	2.27 [.39-13.27]
Psychotic features	16 (47.1)	1 (2.8)	18.65	<.001	31.11 [3.82-253.74]
Seasonal pattern	14 (41.2)	6 (16.7)	5.15	.023	3.50 [1.15-10.63]
Mixed features	11 (32.4)	8 (22.2)	.91	NS	1.67 [.58-4.85]

* The analyses repeated according to the final clinical diagnosis of BDs resulted statistically significant the same, with the exception of mixed features during (hypo)mania, GMC/drug-related MDE, and seasonal pattern of MDE

The comparisons of rates of non-overlapping mixed symptoms and behavioral equivalents during (hypo)mania were made. **Table 24** reports those mixed symptoms whose χ^2 statistics resulted statistically significant or near the significance. (Hypo)manic mixed states in BDI seemed to be associated more frequently than soft BDs to insomnia (p=.075), reduced participation to usually appreciated activities (p=.001), self-injurious behavior (p=.066), avoidance of social situations or specific stimuli and persons (p=.016), affective flattening (p=.068), anxiety symptoms (p=.001) and reduced social responsiveness (p=.081). The same comparisons according to the clinical diagnosis evidenced that insomnia, affective flattening, self-injury and reduced social interactions did not result significant anymore.

Table 24: Mixed features during (hypo)mania: comparisons between Bipolar Disorder type I and soft bipolar spectrum disorders according to SPAIDD-M definition*

Clinical features **N (%)**	**BD I** **N=36**	**Soft BD** **N=34**	**χ^2**	**p**	**OR [95% CI]**
Non-overlapping SPAIDD-M behavioral equivalents of depressive equivalents during (hypo)mania*					
Insomnia	12 (35.3)	6 (16.7)	3.18	NS (.075)	2.73 [.89-8.39]
Reduced participation	18 (52.9)	6 (16.7)	10.21	.001	5.63 [1.86-16.99]
Self-injury	11 (32.4)	5 (13.9)	3.38	NS (.066)	2.97 [.91-9.72]
Avoidant behavior	9 (26.5)	2 (5.6)	5.78	.016	6.12 [1.22-30.83]
Affective flattening	3 (8.8)	0 (0.0)	3.32	NS (.068)	
Anxiety	22 (64.7)	9 (25.0)	11.17	.001	5.50 [1.96-15.43]
Reduced social interactions	8 (23.4)	3 (8.3)	3.05	NS (.081)	3.39 [.82-14.04]
Relative total score depressive features during (hypo)mania, Mean (SD)	.19 (.13)	.07 (.11)	2.46	<.001	

* The analyses repeated according to the final clinical diagnosis of BDs resulted statistically significant the same, with the exception of: insomnia, self-injury, affective flattening, and reduced social interaction.
**The comparisons relative to the following depressive symptoms and equivalents appearing during mania are not reported as far as not significant differences were detected: depressed mood, reduced pleasure and interest, weight gain, hypersomnia, psychomotor retardation, reduced energy and fatigue, guilt feelings, easiness to cry, altered appetite, somatizations, indecisiveness and doubt, abstractive thinking decline, memory issues, reduced drive to leave home, pica, apathy.

CHAPTER 4

4. DISCUSSION

4.1 Characteristics of the sample

The primary aim of the present study was to evaluate the psychometric properties of the SPAIDD-M, a tool for the diagnosis of depressive and bipolar disorders in persons with ID and LF-ASD, based on adaptation of DSM-5 diagnostic criteria. To this purpose, 233 persons with ID of different severity level were randomly or consecutively recruited to undergo an assessment protocol including the SPAIDD-M. As shown in Tables 2, 3, 4, and 5, participants were grouped according to the following three ID levels, 1. BIF and mild ID; 2. moderate ID; 3. severe and profound ID, in order to facilitate the check of sample homogeneity for socio-demographic, physiological, familial, medical and psychiatric background characteristics. . All the among-groups comparisons demonstrated high homogeneity of the sample. The distributions of gender, age and BMI were similar across the groups as well as the main socio-economic features. As expected, BIF/mild ID individuals showed higher social adjustment, educational level, and occupational experiences. They also included a higher number of offenders, even if to a lesser extent in comparison to most of rates in the literature (Lindsay et al., 2013). Regarding the personal physiological anamnesis, the group with severe/profound ID showed higher rates of abnormalities in the first physiological acts after birth and delay in psychomotor, locomotion and language development as well as higher rates of sensory impairments, motor disabilities, epilepsy and gastrointestinal disturbances, which are comparable to those reported in previous studies (Kwok and Cheung, 2007). It has to be noted that immunity-related problems, including allergies and autoimmune diseases, resulted significantly more common in the BIF/mild ID group. The relationship between immunity dysregulation, mostly at the CNS level, and the development of a variety of neurodevelopmental and psychiatric disorders is a field in expansion. For example, immunity-mediated processes, genetic and epigenetic correlates have been implicated in the etiopathogenesis of ASD (Ashwood and Van de Water, 2004). It is possible that, early severe events may impact the neurodevelopment at a level that macroscopic anatomical alterations and severe disruption of most cognitive and motor functions subside most forms of moderate to profound ID. By the contrary, it is possible that milder forms of cognitive impairments, frequently without the detection of imaging abnormalities, may have a more subtle and functional underpinning. The involvement of SNC and general immunity dysregulation at this level is one of the most intriguing hypotheses.

The sample representativeness of the population with ID and LF-ASD resulted to be quite low. In fact, the sample shows a preponderance of participants with moderate-to severe ID while this portion is the lowest in the real-world population. The sample also shows higher percentages of mental health issues and psychotropic medication. Nevertheless, having a sample representative of the real population with ID and LF-ASD was not foreseen in the study design and not relevant for the study aim, since the SPAIDD-M is addressed to persons with high insight and communication impairment. The study design included a random/consecutive sample as meant to be an unbiased representation of the population with ID/LF-ASD attending a clinical service qualified for psychopathological assessment. It was considered a fair way to select a sample from a larger population

since every member of the population with that specific assessment need has an equal chance of getting selected.

A sampling bias linked to this last point refers to the sources of recruitment: half of participants with moderate-to-profound ID were recruited in residential facilities, whereas a similar percentage of those with BIF/mild ID were enrolled in rehabilitative centers and clinics specialized in evaluation of mental health issues in persons with ID and LF-ASD.

In the overall sample entering the study the prevalence rate of co-occurrent psychiatric disorders is 50%, confirmed by internal diagnostic orientation, and the use of psychotropics drugs is around the 70%, particularly anticonvulsants and antipsychotics (around 50% for both). It has to be noted that many patients were under polypharmacy, including add-on treatments with mood stabilizers, multiple antipsychotics, benzodiazepines, and antidepressants, which was not explained by specific diagnostic formulation, not even completed yet at the recruitment time. Unfortunately the association of several compounds is quite common in non-specialized clinical settings and can result from urgency-based management strategies, inattentive prescribing, lack of follow-up of medication use, , wide-spread recourse to off-label prescriptions, lack of specifically addressed evidence-based guidelines , and pressuring to prescription by clients, family members or staff members, who are often insufficiently informed or trained on advantages and risks of drugs use (Bertelli et al., 2018).

Of course medication issues are in general strictly related to diagnostic issues, which are very frequent in non-specialized contexts, especially in reference to persons with higher cognitive and communication impairment (Bertelli, 2015, Bertelli et al., 2015, Costello and Bouras, 2006, Matson and Russell, 1994, Moss et al., 2000, Reiss and Szyszko, 1983). These diagnostic issues are confirmed also by our study findings, with study entry overall psychiatric comorbidity being significantly higher in participants with BIF-to-moderate ID than in those of severe-to-profound degree (see **Table 5**). Indeed, after the deep appropriate assessment foreseen by the study protocol, these differences resulted to be no more statistically significant, with prevalence rates of overall psychiatric comorbidity being similar across the three groups. Diagnostic issues for study entry data were corroborated by results of the detailed analysis of discrepancies between entry and final diagnoses, which show partial or complete mismatch not only for around 40% of participants with severe/profound ID, but also for around 50% of those with moderate ID.

4.2 Psychometric properties of SPAIDD-M 1.2

The SPAIDD-M final version (1.2) showed a fair face validity as indicated by most of the evaluators as well as, indirectly, by its good psychometric properties. Reliabilities between different evaluators and across time resulted to be more than acceptable. The former, calculated through Cohen's K coefficient, was never lower than .575, with a mean coefficient of .713, confirming that, in the complex, the error variance related to the attribution of the scores and the subjectivity of evaluators was poorly significant. Similarly, the stability over time of the attribution of the scores resulted to be very good, as shown by Pearson's r and Kendall's τ-b correlation coefficients being never lower than .77.

Another psychometric property considered was the internal consistency of the tool. All the 65 items relative to symptoms and behavioral equivalents as well as chronological, clinical and course specifiers, resulted to be highly interrelated, as demonstrated by the high value of the Cronbach'α score (.937). The 33 items relative to mixed features showed a lower but equally good consistency (Cronbach'α=.876).

The criterion validity for the major depressive and (hypo)manic episodes was evaluated by two ANOVA analyses comparing the means of SPAIDD-M general and area scores with the clinical overall and specific scores, based on DSM-5 criteria. This method evidenced an excellent criterion validity for all the 9 criteria of the MDE defined in SPAIDD-M as well as for the total mean score. This result was replicated for the (hypo)manic episode for which we considered DSM-5 criteria A and B and the total mean score. We decided not to include mixed features in this analysis as the difficulties met by a certain number of evaluators in the completion of this part of the tool and the lack of previous research to reference to, challenged the full operationalizability of this construct. Further research on larger samples is surely needed on these common but neglected clinical presentations. Thus, it has to be noted that results relative to mixed features and expressed below have to be considered as a first explorative research attempt.

Subsequently, we performed a factorial analysis to identify the number and type of factors explaining the variance of the full instrument. The first four main factors resulting from the factorial analysis explains the 37.21% of the variance in the tool and appeared to explain the differences among items. The first factor, explaining alone around the 20% of the variance was characterized by almost all the items pertaining to (hypo)mania. Here are included not only the "full-blown" (hypo)manic symptoms and equivalents, but also a number of those we had considered as overlapping with depression in ID. Excluding irritability, psychomotor agitation and restlessness, aggressiveness, and impaired judgement, the items relative to affective lability and substance abuse seemed to actually belong to the excitatory dimension. As far as this analysis confirmed the strength of the manic construct proposed in SPAIDD-M, some hypotheses could arise. Indeed, according to one of the initial hypotheses that mood episodes in ID may have an atypical presentation including the association with behavioral problems, this factor actually includes a variety of PBs such as aggressiveness, substance abuse and addiction-related behaviors, hypersexual behaviors, defiant and antisocial conducts, manipulation and exploitation especially directed to peers, and excessive research of social interactions. Other symptoms and equivalents, formally pertaining to the depressive cluster, belong to this factor, specifically insomnia, reduced participation to activities previously appreciated and tendency to cry. Noteworthy, these latter items were frequently reported by evaluators as occurring during the (hypo)manic episode and they often characterized mixed manic phases. Considering the association to this factor to affective lability, it could be speculated a "multistage" link between emotional dysregulation often characterizing the basal functioning of persons with neurodevelopmental disorders and BDs, but also its pathoplastic effect on the presentation of the episode assuming a mixicity figure (Mazefsky et al., 2013, Purper-Ouakil et al., 2017, Shaw et al., 2014, Vannucchi et al., 2019a).

The second factor, explaining around the 6% of the variance, account for depressed mood and reduced pleasure and interests: thus, it can be identified as the "depressive factor". It also includes apathy as well as symptomatic

and behavioral equivalence as well as increase of indecision, rigidity and adhesion to routines, reduced participation and refuse of social interactions. Importantly, it also includes the item relative to catatonic symptoms and disorganization of language and behavior. It has to be noted that the evaluation of catatonia in SPAIDD-M does not include the symptoms of excited catatonia, but only a limited number of more characteristic signs, such as posturing and waxy flexibility.

The third factor explains the 5% of the variance and has been identified as a "non-mood related depressive factor" as it includes a variety of symptoms and behaviors belonging to depression but unrelated to depressive mood. It is composed by symptoms and equivalents pertaining to energies and psychomotor activity disturbances, neurovegetative symptoms regarding appetite and sleep, cognitive and memory worsening, perceptual and though abnormalities. As in the case of the manic factor, here we can find grandiosity and disorganization which are among the mixed symptoms more frequently reported during depression in patients with mixed depressive episodes. It is very suggestive that the main construct of depression can be decomposed in two factors with almost equal weight: this finding may suggest that, at least in persons with ID, the weight given to the presence of depressed mood to make the diagnosis, should be reconsidered.

Th fourth factor accounts for the 4.5% of the variance. This factor is inversely correlated to most anxiety and related symptoms and behavioral equivalents, and it includes excessive research for social interaction and impairment of memory. It is possible to interpret this factor as a secondary manic-related factor or impulsivity-related.

The last psychometric property we evaluated was the concurrent validity. We used two different procedures to make this evaluation, but it has to be considered that the lack of a fully comparable tool, validated in Italian language, and allowing the diagnosis and differential diagnosis of MDs in the ID population, reduced our opportunities to have an irreproachable validation.

The first procedure provided the correlation of the SPAIDD-M main diagnoses (MDD, BD I; BD II and BD otherwise specified) with the corresponding DSM-5 based diagnoses. We excluded persistent depressive and cyclothymic disorders given their low rates in the sample. Other confounding factors were considered, such as the difficulties to clinically distinguish in this sample mild long-lasting dysthymic pictures from antipsychotic-induced depressive-oriented mood alterations. On the other hand, in a population with a high level of basic emotional dysregulation the diagnosis of cyclothymia *strictu senso* could be questionable. The correlation among SPAIDD-M and DSM-5 diagnoses resulted very strong and strong for BD I and BD II ($r>0.7$). The correlation value of the MDD diagnosis was little bit lower, at the highest limit of moderate correlation range. This could be due to the fact that a number of persons diagnosed by SPAIDD-M as having MDD, were reframed as having BD otherwise specified or schizoaffective disorder, depressive type. The diagnosis of BD otherwise specified was that with the lowest correlation value, anyway considered a moderate correlation.

The second procedure, carried out to check the concurrent validity of the SPAIDD-M, involved the correlation of SPAIDD-M diagnoses of depressive and (hypo)manic episodes with the DASH-II subscales for depression and mania, respectively. Although Pearson's and Spearman's coefficients resulted to be both statistically significant, the Spearman's one was higher. In the interpretation of these latter results, it has to be kept in mind

that whereas SPAIDD-M provides a lifetime evaluation, DASH-II is aimed to evaluate a brief period before the assessment. Moreover, the DASH-II is mostly addressed to lower levels of ID: as a consequence, the behaviors and symptoms investigated in the DASH-II items are very sensitive and specific for this subpopulation, but they could not be considered fully appropriate to investigate psychopathology higher functioning subjects. In this perspective and as demonstrated above, SPAIDD-M can give reliable results independently from the severity of ID. By the contrary, DASH-II has the advantage it can be easily used as a follow-up measure and it gives estimation of the severity and impact on adaptation of the symptoms and behaviors.

4.3 Mood Disorders in persons with intellectual disability and low-functioning autism spectrum disorder.

The prevalence rate of the final clinical diagnosis of overall MDs in our sample was 44.2%. This rate is much higher comparing to the rates around 5% for DDs and 2.5% for BDs found in the literature relative to large ID population-based studies (Cooper et al., 2007a, Deb et al., 2001a). A recent metanalysis about the prevalence of co-occurring mental health diagnoses in the autism population and including one hundred studies reported prevalence rates for DDs and BDs of 11% and 5%, respectively (Lai et al., 2019). Nonetheless, this rate can be considered aligned to the results of studies performed in clinical settings (Charlot et al., 2007a). In our sample, the clinical diagnosis of MDs was not associated to differences in main demographic features. Most differences were identified regarding familial and personal psychiatric comorbidity. In fact, MDs were associated to higher rates of overall psychiatric comorbidities in family members. Although the rates for individual psychiatric categories in relatives were all higher in the MDs group comparing to the group without MD, none reached the statistical significance. For example, the OR for familial DDs was 2.24. Familial BDs (not reported in **Table 10**) rated 22.7% in MDs participants, about doubled comparing to the 11.3% of the comparison group. These data are in agreement with the current literature regarding the general population as well as ASD (Bolton et al., 1998, DeLong, 1994, DeLong, 2004, Piven and Palmer, 1999, Song et al., 2015, Vandeleur et al., 2014), whereas systematic data regarding the familial psychiatric load in individuals with ID are substantially lacking. It is possible that the high prevalence of MDs in the sample as well as the high morbidity of the comparison non-MDs group may have contributed to the non-achievement of the statistical significance.

According to the literature regarding the general population, MDs probands in our sample showed prevalence rates of co-occurring psychiatric disorders higher than no-MDs individuals, with an OR=2.58 (p=.011). MDs in this population seemed to be associated to ADHD, OCD, ODD, substance abuse disorders and BED. This pattern of comorbidities is well-known in average IQ children (Masi et al., 2006a, Donfrancesco et al., 2011, Masi et al., 2006b, Hazell, 2010, Sonneville et al., 2015), but also in adults, at least for BED and addiction (Maremmani et al., 2006, Vannucchi et al., 2014b). This result stresses the concept of how actual developmental and emotional levels may have a pathoplastic effect on the expression of PDs in adults, whose clinical picture and management complexities may resemble those found in children more than the pathways typical of their average IQ peers (Bertelli, 2015, Bouras and Drummond, 1992). The higher load of further

psychopathology related to the co-occurrence of MDs in ID was also confirmed by the higher mean raw scores of almost all the DASH-II psychopathological dimensions. The prevalence of personality disorders and specifically those of the cluster C was also higher in individuals with MDs. No data are available in ID and LF-ASD population to compare our data accounting for the co-occurrence of MDs. Moreover, it has to be considered that the construct of personality disorders is extensively criticized by most researchers and clinicians depending on the idea that the full structuration of personality requires a complete emotional development. Thus, it could be more correct, as for young adolescents, to cautiously speak about personality traits and organization. Further specific studies would be needed to address the large overlapping areas between true pathological personality traits and the "normal" rigidity and neurovegetative over-reactivity as well as tendency to isolation characterizing persons with ID and LF-ASD. Nonetheless, both of the groups should have suffered for these limitations and it is interesting that MDs would be associated to basic anxiety and anankastic traits in such a population.

As expected, MDs were associated to much higher load of psychotropic drugs: the presence of any MD leads to a 9-fold increase of the probability to assume psychotropics of all psychopharmacological classes. By the contrary, no significant differences emerged regarding the side effects of medications between the two groups, although MDs subjects had a 4-fold higher risk to develop psychiatric adverse effects under antidepressant treatment. This is not surprising considering the high prevalence of BDs in our sample. By the contrary, that these results did not achieve the statistical significance could be attribute to the fact that all the use of psychotropics was widespread in the overall sample, independently from the diagnosis, and ID individuals are known to be more vulnerable than the general population to side effects (Bertelli et al., 2018).

When examining the clinical features of MDs in ASD subjects of our sample, comparing to the non-ASD subjects, we found ASD to be associated to higher prevalence of overall MD diagnoses and specifically BD I. ASD was also associated to mixed features of both MDE and (hypo)manic episodes, dysphoric mania, catatonia, seasonal pattern and rapid cycling course (Lai et al., 2011, Lainhart and Folstein, 1994, Vannucchi et al., 2019b). As regards the response to psychotropics, the ASD diagnosis was significantly associated to the development of affective flattening and depressed mood. This is a very important aspect as far as it may contribute to the misdiagnosis of BD forms in ASD as SSDs (Skeppar et al., 2013). Although our data are not sufficient to state ASD to be an additional risk factor for the development of MDs at all, it can be hypothesized the association of ASD with a bipolar diathesis. The phenotype of BD in ASD was characterized by higher severity indices including the prevalence of type I forms, mixed states and rapid cycling. It is possible that the severe emotional dysregulation characterizing most of the ASD patients at high risk to develop MDs may mediate this peculiar and complex pattern of affective manifestations (Joshi et al., 2018).

4.4 Depressive and Bipolar Disorders in Intellectual Disability and Low-Functioning Autism Spectrum Disorder

In our overall sample, as for the general psychiatric comorbidity, the prevalence rates of MDs and specific DDs and BDs diagnoses according to the SPAIDD-M assessment did not differ across the three ID groups.

This is important as it confirmed the suggestions of some researchers that even lower functioning ID persons may suffer for the complete span of affective disorders (Cooper et al., 2018, Fletcher et al., 2016, Hurley, 2006, Sovner and Hurley, 1983). The repetition of the comparative analyses on the subsample regarding those participants who had completed the full study protocol, and considering different definitions of DDs and BDs (SPAIDD-M, adapted DSM-5 criteria, and clinical procedure) confirmed this finding. The comparison of the prevalence rates per specific MD diagnosis evidenced a diagnostic trend across the different diagnostic procedure. As expected, we found the higher rates with SPAIDD-M assessment: indeed, as far as it equates typical affective symptoms to behavioral equivalents and although a rigidly DSM-5 based structure, it resulted highly sensitive and also inclusive of very atypical syndromic presentations. It can be questionable that such a sensitivity could lead to over-inclusiveness. Differently from what suggested by previous research, we found higher rates via the application of DSM criteria than with the clinical diagnostic procedure (Cooper et al., 2018). This discrepancy with the literature could be justified by the fact that, given the main purpose of the study to cross-validate SPAIDD-M with DSM-5 criteria, as explained in the method section, the application of DSM-5 criteria extensively took into account the adaptations and examples of DM-ID-2 (Fletcher et al., 2016). It seems plausible that this enlargement may have improved the diagnostic sensitivity. The rates resulted from the clinical diagnostic procedure were highly superimposable to those of both SPAIDD-M and DSM-5, rather for DDs. It has been already suggested that a considerable number of those participants with a SPAIDD-M assessment positive for DDs had been reframed as has schizoaffective or cluster A personality disorders. Moreover, given the large use of antipsychotics in our sample, it resulted very hard to differentiate a primary DD from syndromic pictures secondary to use of such medications. The reduced potential for differential diagnosis with the above-mentioned conditions, represents one of the major limitations of the current version of SPAIDD-M. However, it has to be considered that the SPAIDD-package tools are thought to be used "surgically" in combination one each other, just in order to overcome these diagnostic issues.

Multiple statistical analyses were made on the subsample of the 110 participants diagnosed as having MDs with the SPAIDD-M, with the aim to identify differential clinical profiles of DDs and BDs. Depressive and bipolar patients did not result different regarding socio-demographic and most physiological variables. Even the medical comorbidities had similar rates between the two groups, rather obesity, significantly associated to BDs. This result might be the resultant of multiple factors interacting one each other: in fact, the BDs diagnosis was associated to the co-occurrence of BED and larger use of antipsychotic medications. Although the comparison of antipsychotic-induced weight gain and metabolic side effects did not achieve the statistical significance, BDs subjects appeared at higher risk than DDs. BDs were associated to higher prevalence of overall mental health disorders among in relatives, specifically and according to the expectations of BD and personality disorders, but also psychotic and eating disorders although the statistical significance was not reached. Coherently with the comorbidity profiles of different MDs in the general population, we found DDs to be associated to comorbid anxiety disorders (Charlot et al., 2007b, Fletcher et al., 2016, Hurley et al., 2003, Marston et al., 1997), mostly GAD, whereas BD presented a complex pattern of comorbidities including

ADHD, eating disorders, impulse control disorders and dysfunctional personality organizations (Hazell, 2010, Masi et al., 2006b, Mavromatis, 2000, Sonneville et al., 2015).

As mentioned above, it seems to exist a relationship between affective disorders, eating dyscontrol and ADHD. In our study this relationship seems to be mainly related to a bipolar diathesis as far as demonstrated by the regression model (see **Table 18**), indicating that the belonging to the SPAIDD-M defined BDs group was predicted by the co-occurrence of BED and ADHD as well as the higher familial load for mental health issues. By the contrary, the co-occurrence of GAD predicted the diagnosis of DDs. When considering the clinical diagnosis of MDs rather than the SPAIDD-M assessment, the diagnosis of BD was predicted by ADHD and family history for psychiatric disorders, whereas DDs were predicted by GAD and the presence of family members with ASD (see **Table 19**). It can be cautiously speculated that there would be a continuity among different neurodevelopmental disorders and that the co-occurrence of psychiatric disorders should be interpreted through a neurodevelopmental perspective: differential pathways of central nervous system development, through differences in prevailing cognitive, executive and subcortical dysfunctions, may carry out a significant pathoplastic effect subsiding differential clinical, psychiatric and behavioral phenotypes in adults with ID. Familial predisposition, thus differential genetic underpinnings, may have a weight in determining both the developmental pathways as well as the comorbidity patterns of neurodevelopmental and psychiatric disorders. In this perspective, the affective dimension and MDs diagnoses should be better explained as a continuum rather than separated entities. This hypothesis might be cautiously confirmed by the evidence in our study that DDs and BDs did not show significant differences in most clinical illness-related variables considered in this sample. For example, no differences emerged in the clinical and course specifiers of the MDE between the two diagnostic groups.

Noteworthy, DDs and BDs were not associated to differences in the prevalence of mixed depressive episodes and the type of counterpolar symptoms. Indeed, mixicity was very common in both the diagnostic groups, far higher than the rates reported in the general population (Vieta and Valenti, 2013). Even considering that mixed features are poorly operationalized in the ID population and the results of our study have absolutely to be considered inconclusive concerning this point, some considerations can be made. On one hand, our results gave a confirmation to the widespread impression of clinicians and experts that mood episodes in ID, as well as in other neurodevelopmental disorders, actually have more frequently mixed clinical presentations (Felstrom et al., 2005, Reid and Naylor, 1976, Ruedrich, 1993). This unrecognized aspect may lead to over-representation or accentuation of aggressiveness, self-injury, impulsivity and oppositional-defiance during major affective episodes, particularly depression: this might be a potential source of misdiagnosis and it may be related to inconsistent psychopharmacological strategies. On the other hand, our result challenges the concept of "mixed features specifier" as conceived in DSM-5: at least in the ID population with MDs, mixed features seem to represent a core feature of the illness more than a mere specifier, and in highly unstable patients it could appear artificial and hard the distinction between opposite polarity episodes as far as in most cases depression and excitement are present at the same in time with various intensity or rapidly alternating. A result further supporting this hypothesis was derived by the comparisons of clinical and course features of

BD I with soft bipolar spectrum disorders. No clinical and course differences were identified, rather for psychotic symptoms to be associated by definition to BD I. However, the analysis regarding the type of depressive and mixed equivalents present during the manic episode comparing to hypomania (see **Table 24**), revealed that anxiety symptoms, self-injury, reduced interests and participation to activities, and social withdrawal were more common during mania. This result could suggest the validity of the constructs of the full-blown mixed episode and affective illness characterized by mixed episodes as a specific phenotype of MD, as they were conceived in the classical literature (Kraepelin, 1896, Weygandt, 1899). In the continuity hypothesis mixicity could also be considered a severity index. Certainly, these are speculations based on a pioneer and inconclusive work; further research on larger samples are needed to explore in depth this topic.

CHAPTER 5

LIMITATIONS OF THE STUDY

Several limitations have to be taken into account in the interpretation of the present study and concerns regard both the main and the secondary objectives.

The method employed for the validation of SPAIDD-M, particularly the procedure relative to test the concurrent validity, suffered for the lack of a full comparable tool validated in Italian language. Thus, definite conclusions about its sensitivity and specificity could not be drawn. Moreover, both the application of adapted DSM-5 criteria for DDs and BDs and the clinical diagnoses have not followed a blinding procedure and this represents an important methodological weakness. On the other hand, the administration of the study protocol and the final diagnostic conclusion have been relied on fully trained psychiatrists with a specific expertise in the ID field. Considering the literature evidencing the great difficulties of the psychiatric diagnostic process in persons with ID, mostly those with greater cognitive and communication impairments, this can be considered at some extent a strength.

Another possible reason of debate could be represented by concept of behavioral equivalence itself and its relationship with psychiatric syndromes, observed behaviors and problem behaviors. In chapter 1 the concerns at this regard have been extensively discussed, but here it is necessary to mention that it could be arguable a large related selection bias. Indeed, the study was mainly aimed to validate a diagnostic tool, thus we tried to recruit a sample including proportional numbers of subjects with low and high risk to be diagnosed as having a MD. Nonetheless, it could be argued that such a recruitment procedure selected those individuals who were already known to have complex behavioral disturbances and to experience mental health issues, as confirmed by the data. The resulting demonstration that behavioral equivalents are a reliable mean to diagnose psychiatric disorders in persons with ID, mostly those with lower functioning, would be argued to be tautological. However, it has to be noted that at the beginning of the study only the 28% of the participants with severe to profound ID had received a psychiatric diagnosis and only for this subgroup the rate was doubled at the end of the study achieving a prevalence level similar to those reported for the other ID groups. This observation, together with the parallel use of adapted DSM-5 criteria and the fact that behavioral equivalents were accurately clustered with other types of “more classical” affective-related symptoms to describe complex syndromic entities, partially overcome this concern.

A related issue would be that the appearance of behavioal problems might be related to stressful events, thus it could be difficult in some cases to qualify a behavior as reactive or actually related to a psychiatric condition. Actually, the study did not provide the environmental assessment and behavioral analysis usually performed to settle such an issue in clinical practice. Though, the lifetime design of the tool and the evidence that no differences were detected between participants with and without MDs regarding a variety of social, relationship, educational, and economic information collected, suggest that this issue would be considered negligible.

If anything, the possible selection bias conditioned by the main purpose of the study, as well as the referral bias related to the recruitment settings, affected the generalizability of the data to the overall ID and LF-ASD population. The prevalence rates of DDs and BDs, as well as comorbid psychiatric disorders, are related to a clinical population of persons attending specific clinical and rehabilitative services or living in residencies addressed to meet the complex needs of more severely impaired ID subjects. This is an indirect severity index mostly for BIF and mild ID individuals. Unfortunately, an attempt to extend the recruitment to different settings was made via the involvement of multiple partners across the Italian country (e.g. associations of families), but the adhesions resulted very sparse; by the contrary, both the clinicians and the proxies of intellectually disabled persons with mental health or behavioral issues were highly motivated to participate in order to receive a diagnostic refinement.

Even an informant bias has to be kept in mind, shared by any assessing tool using proxies to collect information. The informant bias would not probably influence the rates of disorders: indeed, the bias was bidirectional as some proxy tend to exaggerate the relevance, severity or duration of symptoms and behaviors explored by the tool, while others may show an opposite tendency toward minimization or may have difficulties in remembering or making chronological positioning of the symptoms.

One of the major weakness of the SPAIDD-M, already discussed along the manuscript, was represented by it does not provide the possibility to definitely make a differential diagnosis between primary affective disorders, schizophrenia spectrum disorders and some iatrogenic clinical pictures including affective manifestations related to side effects of psychotropics, mainly antipsychotics. More specifically, the tool resulted positive for depression and mania in many cases we subsequently clinically diagnosed as schizophrenia and schizoaffective disorder. Contrary to the expectations, major issue did not arise with the differential diagnosis between SSDs mainly characterized by positive symptoms and BD I, but mostly between clinical pictures with prevailing negative symptoms and mild long-lasting forms of DDs. Similarly, DDs were poorly distinguished from those iatrogenic clinical pictures related to the side effects of long-duration antipsychotic treatments. However, the latter aspect would not be completely attributable to some weaknesses of the instrument, but perhaps to the poor awareness of most clinicians about the full range of such side-effects and their behavioral correlates or the difficulties in obtaining such a complex information by proxies.

Given all the discussed limitations, our study has some important strengths. The numerosity of the sample was adequate to evaluate the psychometric properties of the tool, even if the optimal number to achieve the goal of full validation would have been 300 participants. The dimension of our sample, in comparisons with clinical samples usually utilized in this field, appeared far acceptable to draw indications regarding the main features and associated characteristics of MDs in adults with ID and LF-ASD. The diagnostic methodology including the comparative use of adapted DSM-5 criteria and another specifically addressed tool, the DASH-II, made the results sufficiently robust.

CHAPTER 6

CONCLUSIONS

The present study was aimed to validate a new tool for the diagnosis of depressive and bipolar disorders in adults with ID and LF-ASD, the SPAIDD-M. The tool was based on the criteria provided by the current classifications of mental disorders (DSM-5), but the formulation of the items and descriptions of clinical features were integrated with adaptations for persons with ID taken from DM-ID-2 and DC-LD as well as with the results of a systematic mapping of the literature regarding the peculiar and atypical manifestations of mood disorders in this population. The tool was a dichotomous-answer questionnaire to be administered to proxies or care givers. It was based on indication of behavioral changes (in quantity or quality) from the baseline and other observable symptoms across time with a significant impact on personal functioning. The theoretical frame was represented by the concept of *behavioral equivalents*, particularly useful for the psychiatric diagnosis in those persons with lower cognitive abilities and severe language and communication impairments. SPAIDD-M, 1.2 version, beyond the good psychometric properties, demonstrated to fairly describe depressive and bipolar disorders in intellectually disabled individuals, and to discriminate different affective disorders from each other, independently from the ID level. Indeed, when comparing the prevalence rates between different ID levels, we found similar percentages across the ID range, which supports the hypothesis that ID persons may suffer from the whole span of mood disorders. Findings of previous studies showing lower prevalence rates in persons with ID compared to the general population, especially in moderate-to-profound ID degree, would be explained through methodological issues and assessment procedures. Moreover, the factorial analysis of SPAIDD-M 1.2 items indicated that behavioral equivalents clustered with other observable symptoms, describing coherently two manic and two depressive dimensions. Thus, our results support the use of behavioral equivalence as an effective integration to the psychiatric diagnostic process.

In our sample the prevalence rates of DDs and BDs resulted to be much higher than in the general population with ID and LF-ASD, this could be attributed to the peculiarities of the study design and results cannot be extended to the all ID population. By the contrary, our sample allowed to delineate demographic, anamnestic, familial and clinical variables associated to MDs. We found MDs to be associated to higher family history of all psychiatric disorders, particularly of MDs. In line with literature on the general population, we found MDs in people with ID to be significantly associated to a variety of psychiatric comorbidities. The comorbidity patterns are quite similar to those found in children average IQ and in young adolescents with MDs more than in adults, confirming that the developmental level may significantly impact on the presentation and trajectory of co-occurring mental health issues. We found ADHD, impulse control and binge eating to be associated to bipolar presentations, whereas anxiety disorders were more commonly associated to depressive ones. LF-ASD was associated to higher rates of all MDs, especially BD I, and to symptomatic peculiarities, such as catatonic and mixed features. In a perspective of neurodevelopmental vulnerability, persons with LF-ASD with high baseline levels of emotional dysregulation may be regarded as the persons within the autism spectrum with highest risk to develop severe bipolar illness.

We found few differences of clinical and course phenotypization between DDs and BDs, although the small sample size, which is probably insufficient to draw definite conclusions on this point. DDs and BDs resulted to be both characterized by high rates of catatonia, psychotic features and seasonal pattern. Moreover, around 23% of BD patients showed a rapid cycling course of the illness. All these features, which represent clinical specifiers, may be interpreted as indices of severity, although there are other probable explanations, such as a pathoplastic effect of the basal neurodevelopmental condition on the expression of co-occurring disorders. As far as our knowledge, this is the first study attempting the operationalization of mixed features in the presentations of MDs in adults with ID and LF-ASD. In both DDs and BDs mixed features are much more common in ID (up to around 50%) than in the general population, and the construct of the full-blown mixed episode could depict a high number of clinical pictures than the current DSM categories. This prominence of mixed features in adults with ID and LF-ASD could be interpreted as a result of a complex mood vulnerability linked to the neurodevelopmental alterations and can offer a base for future studies on the utility of a separated model of MDs in respect to a unified one.

Further research with larger samples is needed to identify the actual prevalence and to better delineate specific features of MDs in the general population with ID and LF-ASD.

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