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APPLICATION OF A BROADBAND RATING SCALE (ITSEA) IN UNDER-THREES WITH AUTISM SPECTRUM DISORDER

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Chapter 1

General Introduction and Aims

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by early-onset core impairments in social interaction and social communication, and repetitive, restrictive and stereotyped patterns of interests, activities and behaviors.
The latest revision of DSM (APA DSM-5, 2013) has adopted the umbrella term autism spectrum disorder to contain a group of heterogeneous neurodevelopmental conditions with multiple causes and courses, a great range in the severity of symptoms, and several associated co-morbid disorders, for whom heterogeneous pattern of neuropathology are hypothesized (Lai et al., 2014; Amaral et al., 2008).

ASD is one of the most prevalent forms of developmental disability. The prevalence of autism has incredibly increased (twentyfold to thirtyfold) since the earliest epidemiologic studies. The first one (Lotter V., 1966) reported a prevalence in UK of 4.1 every 10.000.
In the United States since 2000, The Autism and Developmental Disabilities Monitoring Network of the US Centers for Disease Control has collected data to provide estimates of the prevalence of ASD as well as other developmental disabilities among eight year-olds, from up to 14 US centers every two years. Prevalence of ASD reported for the 2008 surveillance year was of 1 in 88 children (CDC, MMWR Surveill. Summ., 2012).The most recent analysis reports a prevalence for the 2010 surveillance year of 1 in 68 children. (CDC MMWR Surveill. Summ., 2014). In 2012 Elsabbagh et al. systematically reviewed the epidemiological reports of autism prevalence and have reported a median worldwide prevalence of 0.62–0.70 % (17/10.000 for AD and 62/10.000 for all PDDs combined). Despite this high prevalence, there is still a great variability in screening, diagnosis and intervention within the same country and among different countries.

In the last decades the research on ASD has seen an utmost growth. The goals are multiple and interconnected: to define the first symptoms, the clinical expression and the developmental course of symptoms; to define the neuropsychological, neurobiological and

etiological underpinning; finally to try to find out the relation between etiological factors, structures, functions and clinical phenotypes.

The research field focused on early manifestations of ASD has increased our knowledge of the first signs (see Zweigenbaum et al. 2013 for a review). The findings have demonstrated the great heterogeneity of core and co-occurrent symptoms, of their onset, course and severity and the involvement of skills across multiple domains in the early development. Studies have also suggested that the diagnosis of autism spectrum disorders (ASD) can be reliably made in the second year of life, and these early diagnoses appear to be relatively stable over time (Chawarska et al. 2009; Rogers 2009).

Multiple reasons motivate the interest in early diagnosis and detection: the increasing prevalence; the growing evidence of the benefits of early intervention (Dawson et al. 2008; Warren et al. 2011; Dawson et al. 2012; Crais & Watson, 2014; Koegel et al. 2014); the possibility to better identify the core nature of the disturb, the brain functions involved, the different kind of onset in order to guide the neurobiological and etiological research (Rogers et al., 2009). The final and main aim is to improve the capacity of early detection and the etiological definition with the purpose, respectively, of secondary and primary prevention (Williams & Brayne, 2006).

Despite the recognition of the utility of early diagnosis and the increasing knowledge of early signs, the early detection and diagnosis still are challenges.
The age of first diagnosis is still reported to be frequently comprised between 3 and 4 years of age (CDC, MMRW, 2014), even if the data about parent's concern report the majority of first concerns before the second birthday (Wiggins et al., 2006; Ozonoff et al., 2009; Daniels et al., 2013).
Different hypothesis have been suggested to explain this delay, such as inadequate screening practice, limited availability to specialized services for children under the age of three, delayed access to specialized service after first communication of concern.
The challenges concerning the early diagnosis are however intrinsic to the clinical expression of the disturb itself:

- the Development during the first years of life progresses at a rapid and sometimes uneven pace across developmental domains (Mossman Steiner et al. 2011), showing a great variability both in typical and atypical development

- the overlapping of symptoms between different neurodevelopmental disorders in early life
- the heterogeneity of severity, onset, course, and constellation of ASD symptoms;
- the heterogeneity of the cognitive, linguistic and communication impairments, social-emotional, behavioral, regulatory problems and sensory processing associated
- the observation that in the early development it is often the absence or loss of typical social development markers that signal the beginning of the ASD diagnosis rather than the presence of atypical behaviours is to be added to all the factors above (Martínez-Pedraza and Carter 2009)
- the fact that, even if advances have been made in the study of biological basis of the disturb, still there are not available biomarkers and the diagnosis remains based on the behavioral observation

As a consequence there is a need to continue to promote the increase of knowledge of the early signs and the identification of tools able to support the characterization and identification of young children with or suspected of an ASD.

The Infant-Toddler Social and Emotional Assessment (ITSEA) is a parent-report measure of social and emotional development. It presents two principal advantages: first, it has been specifically developed for children age 12 to 36 months; second, it measures the development of competencies in addition to the detection of emotional and behavioral problems.
The acquisition of evidence confirming the usefulness of this tool may support its use in screening and clinical assessment of the early developmental age, which still remains a critical period due to the variability intrinsic to development and to the symptoms expression, as well as in reason of the plastic potential of this period of life.

Aims of the Thesis

In this work the results of the application of an Italian version of the ITSEA in a referred clinical population are reported.
The main aim of this study is to define the profile of ITSEA in children under the age of three (range age 12-35 months) with Autism Spectrum Disorders through its use in a population of children already diagnosed with ASD or referred for a suspicion of ASD which has been subsequently confirmed.
The main research questions are:

- What is the ITSEA profile in Toddlers with ASD like? Is there a typical recognizable ASD profile as proposed by the ITSEA Manual?

  Which are the characteristics relative both to the scales hypothesized to address core autism symptoms and the non-ASD scales?

  Are there recognizable different profiles in relation to gender, age, developmental level?
- Does ITSEA profile distinguish between ASD toddlers and Typical Development toddlers?

  Which are its screening accuracy, sensitivity and specificity? Does the accuracy change relative to age (younger and older than 24 months)?
- Does ITSEA profile distinguish between ASD toddlers and others developmental concerns (i.e. Developmental Delay and other Mental Health Disorders) in toddlerhood?

Outline of the thesis

The thesis is composed of two parts. In the first part the theoretical background is retraced through the literature regarding the expression of Autism Spectrum Disorders in the first years of life, namely the second and third years, (Chapter 2) and the literature concerning the screening and assessment tools (Chapter 3); finally the study's object of analysis, ITSEA, is presented through its description (Chapter 4.1) and the review of literature relative to the application of ITSEA and of its brief version (BITSEA) in Autism Spectrum Disorder (Chapter 4.2).

In the second part of the thesis the results of the clinical study are reported: the description and analysis of the ITSEA profile in an ASD toddler sample, in comparison with the profile provided in the ITSEA Manual for an Autistic Disorder group, and in the subsamples defined by gender, age and developmental level (Chapter 5.2.1); the comparison between the ASD group and a Typical Development control group (Chapter 5.2.2) reporting results concerning the accuracy, sensitivity and specificity in both the overall group and in the younger and older than 24 months subgroups; the clinical application in respect to other clinical conditions (Chapter 5.2.3): comparison between the ASD and a Developmental Delay group and a group of children with other Psychiatric Disorders; comparison with the overall non-ASD group reporting data about accuracy, sensitivity and specificity; summary of findings and final discussion (Chapter 6).

Part 1

Background

Chapter 2

Autism Spectrum Disorder in the first three years of life

Chapter 2.1

EARLY SIGNS

The research focused on the early development in ASD has been based during the last decades both on retrospective studies, as like parents reports and early home videotapes (i.e. Baranek, G.T. 1999; Maestro et al., 2001; Maestro et al, 2005; Palomo et al., 2006; Ozonoff et al., 2011.), and prospective studies of children at elevated risk for ASD (i.e. Zwaigenbaum et al., 2005; Rogers, 2009; Ozonoff et al., 2010).

As summarized in Zweigenbaum et al. (2013), retrospective studies have constituted the first insight into the knowledge of first signs. They however present some limitations: parental reports of early symptoms of ASD are subject to recall biases; pre-diagnostic home videos may be subject to other biases related to sampling, however they continue to generate important information about early ASD manifestation. Prospective research designs focused on high-risk infants present the methodological advantages of: standardized measures; longitudinal data to map initial trajectories of symptom emergence; possibility of include experimental measures (e.g., eye tracking, evoked brain responses) that promote the knowledge of underlying developmental processes as well as potential biomarkers. The limitations of prospective studies include the possibility that siblings children may not be fully representative of all children with ASD; developmental delay control groups are needed in order to identify ASD-specific early signs and they are not easy to identify.

With their limits and advantages, these studies have enormously increased the knowledge of autism and the awareness of its complexity and heterogeneity in respect to time of onset, levels of core symptoms, developmental course and associated symptoms.

Previous reviews of early ASD literature share common findings (Zwaigenbaum et al. 2013; Jones et al. 2014): few behavioral findings have been identified in the first year of life; early symptoms are apparent across multiple domains.

The studies focused on early ASD expression have explore development in its overall domains and have taught us that autism is not limited to a social-communication impairment,

rather it is a disorder involving symptoms across multiple domains with a gradual onset that changes both ongoing developmental rate and established behavioral patterns across the first two to three years of life, and typically results in severe social-communication impairment (Rogers 2009). We actually know that ASD is a neurodevelopmental disorder whose first and distinguish markers can be identified during the second year of life. Indeed, according to the present research data, the most reliable and robust differences are detectable by 12 months. Some data, such as that coming from eye gaze patterns studies (Elsabbagh et al. 2012), subtle abnormalities in postural symmetry and in social communication behavior, have been found at 6 months, but to date there are not prospective studies indicating the association between markers detected prior to 12 months of age and a subsequent ASD diagnosis.

Replicated risk markers after 12 months include impairments in social communication (e.g., reduced social orienting/response to name, reduced joint attention behaviors), repetitive behaviors involving body movements and/or atypical use of objects (e.g., intense visual inspection and repetitive actions such as tapping and spinning), and atypical emotional regulation (reduced positive affect and, more variably, increased negative affect) (Zwaigenbaum et al. 2013). Other developmental elements such as the motor development, patterns of language and cognitive development, the self regulation of both the sensory processing, emotional and physiological functions and the attention regulation have been examined and identified as aspects that can differentiate ASD from typical development.

FIRST SIGNS

Zwaigenbaum et al. (2013) propose a comprehensive review, of both retrospective and prospective studies, and they report the findings concerning all the developmental domains explored. We summarize the reported findings following the categories of behavior proposed in the paper, focusing in particular on the findings after 12 months of age.

Social-communication

By 12 months: reduced/atypical orienting to people, specifically people's faces; lack of response to name; reduced eye contact; reduced positive affect including social smiling; fewer communicative gesture including declarative pointing.

Reduced response to name and reduced gazes distinguish between ASD children and Developmental delay children

During the second year: ignoring people and preferring to be alone; reduced peer interest; atypical /reduced social orienting including poor eye contact; reduce orienting to name (by

12-18 months); reduced spontaneous expression and share of positive affect; reduced response to joint attention (15-18 months, even if not specific in case of mild deficits); delays in the acquisition of communicative and symbolic gestures, reduplicated babbling, and directed vocalizations (by 12-14 months)

Gaze, affect-related behaviors, reduced interest in peers and reduced showing and communicative gestures distinguishing between ASD children and Developmental delay children by the age of two (differences in responsive smiling at 13-15 months and use of communicative gesture by the age of 19-24 moths).

Repetitive interests and behaviors

By 12 months: similar levels of repetitive motor actions as DD children (differentiating both form TD children); different atypical uses such as rotating, spinning and unusual visual exploration, including intense visual inspection (differentiating from both the DD and TD)

During the second year: higher frequency of repetitive behaviors with objects and with body compared to developmentally aged matched group

Language and cognitive development

By 12 months: lower expressive and receptive language scores on the Mullen Scales of Early Learning (at 12 and 14 months) in ASD high risk infants

During the second year: expressive and receptive language delay; developmental slowing in ASD high risk infants and ASD children of community samples

Motor development

By 12 months: postural control, positional asymmetry (observed since the 6 months of life)

During the second year: lower Fine Motor and Gross Motor scores at Mullen Scales of Early Learning in High risk ASD children

Self regulation and temperament

By 12 months: reduced expression of positive affect and increased distress reactions; abnormal regulation of both affect and visual attention

During the second year: low positive affect and increased duration of attention (specific of ASD high risk infants at 24 months), poor regulation of negative emotions and difficulty with attention control (distinguishing both ASD and non ASD high risk children from low risk children at 24 months)

Atypical regulation of affect and attention surely constitute new interesting model of early ASD symptomatology contributing to the theoretical model of autism as a developmental cascade and progression toward the social-communication impairment that we typical recognize as ASD.

The atypical regulation of sensory processing, emotion and attention and their relation in ASD have been studied in the last years.

Garon et al. (2009) found that high risk infants diagnosed with ASD at 36 months were distinguished from non-ASD sibs and controls by a temperament profile marked by lower positive affect, higher negative affect and difficulty controlling attention and behavior (labeled Effortful Emotion Regulation by the Authors)

Clifford et al. (2013) have found that high-risk infants later diagnosed with ASD were distinguished from controls by a temperament profile marked by increased Perceptual Sensitivity from the first year of life, and increased Negative Affect and reduced Cuddliness in the second year of life. Filliter et al. (2015) found that siblings with ASD demonstrate less positive affect (reduced smiling) than infant siblings without ASD and low-risk comparison infants at 12 months.

Anomalous responses to sensory stimuli has been reported as a future of ASD since first description of the disturb and first person descriptions (Kanners, 1993; Grandin, 1986, 2014). Anyway hyper o hypo responsiveness to sensory input and unusual interest in sensory aspects of the environment have been only recently included in the new diagnostic criteria of ASD in the DSM-5.

Even if a high frequency of atypical behavioral responses to sensory information is reported (Marco et al. 2011), scientific data and opinions about sensory dysfunction in autism are still controversial. "What do we know about sensory dysfunction in autism?"is the question reported in the title of a study published in 2005 (Rogers & Ozonoff, 2005) and it still remains open. Research studies concerning sensory responsivity in ASD have shown that persons with ASD tend to show more than one type of Sensory Modulation Disorder, often showing a combination of hypo and hyper-responsiveness to sensory stimuli with a prevalence of hypo responsiveness during early childhood (Rogers &Ozonoff, 2005; Ben-Sasson et al., 2009; Baranek et al., 2013). Avoiding and sensitivity manifestations are considered two types of hyper-responsivity; sensory seeking has been hypothesized to modulate both the under and the over-responsivity, but it is not always present (Liss et al., 2006; Ben Sasson et al. 2008). In their meta-analysis Ben Sasson et al. (2009) report a trajectory characterized by an increase in the frequency of sensory behaviors overall, in over-responsivity and in seeking up

to age 6–9 years, and a decrease there after; for under-responsivity a consistent course wasn't found. A positive correlation of over-reactivity with age was previously revealed also by Liss et al. (2006).

The challenges related to the detection of difficulties in sensory processing and in the definition of their role in Autism Spectrum Disorder can partly referred to the lack of a consensus on the appropriate tool for measuring the sensory processing in early childhood and this difficulty is in part due to the challenge of defining constructs in sensory processing (Eeles et al., 2012). Moreover, as suggested by Grandin (2014), what we can measure is the observational data regarding exterior reaction to stimuli but we cannot certainly know what kind of anomaly of the sensory processing is causing that typology of response. For example Ben-Sasson et al. (2007) found a correlation between low registration and avoiding, hypothesizing that low registration may be an attempt to avoid overstimulation; more in general they found a mixed pattern of responsiveness that has been subsequently confirmed (Ben-Sasson et al. 2008) and that could be explain by a compromised ability to regulate and modulate responses.

The presence of an anomalous sensory processing has recently been confirmed in a prospective studied (Germani et al., 2014) were high-risk infants diagnosed with ASD were found to have more difficulty with auditory processing (i.e., responses to auditory stimuli) and lower registration (i.e., lacking sensation awareness) compared to controls (non ASD high risk infants and low risk infants).

The sensory patterns revealed in autism have been described to relate to social-communication impairment (Foss-Feig et al., 2012; Baranek et al., 2013), to restricted and repetitive behaviors (Foss-Feig, 2012) and to affective symptoms (Ben-Sasson et al., 2008, Green et al., 2012).

In 2013 Baranek et al. explored the sensory Hypo-responsiveness, its relation to sensory orienting in both social and nonsocial contexts in young children with autism, and the potential associations between hypo responsiveness and broader developmental outcomes. The results showed that the autism group oriented less to all sensory stimuli compared with controls and this was particularly evident at younger mental ages; they also found support to associations between sensory responsiveness and joint attention indicating that lack of orienting to both social and non social stimuli is associated to lower joint attention and this is particularly evident at lower mental ages. The Authors suggested that their findings were consistent with theories by Mundy and Collegues (2010) that proposed the deficit of two attentional neural networks in autism, a posterior system supporting early developing

generalized sensory orienting and response to joint attention and an anterior system supporting later-developing and more volitional social-cognitive behaviors related to orienting attention.

ONSET PATTERNS

Considering all the reported studies, and as it has been in particular demonstrated by longitudinal studies, a great individual heterogeneity relative to the early markers' onset and the developmental course of ASD symptoms must to be taken into account (Zwaigenbaum et al. 2013; Trembath & Vivanti 2014).

Both home videos and prospective studies have been used to analyze the trajectory of onset. Ozonoff et al. (2011) analyzing social-communication behavior from home videos taken between ages 6 and 24 months found three typologies of trajectories: the 'early onset', the 'regression', the 'plateau' trajectory (to note that there was surprisingly poor agreement between classification based on analyses of home videos and parents' retrospective reports at age 3 years and that the regression was noted prior to 12 months). Landa et al. (2007) in a prospective study comparing early onset high risk infants, later onset high risk infants, non-diagnosed high risk infants and low risk infants, found that the later onset high risk infants truly appeared relatively asymptomatic at 14 months, differing from non-diagnosed HR infants only on the basis of frequency of gaze shifts, whereas, many symptoms were present by 24 months, leading to suspected ASD diagnosis. As proposed by Ozonoff et al. (2008, 2010), Rogers et al. (2009), Zwaigenbaum et al. (2013) the pattern of onset, more than distinctive categories of early onset, plateau and regression, should be considered as a continuum. The extremes are constituted by the traditionally defined, prototypical early onset and regressive cases, but many intermediate phenotypes are contained and they characterized by slower or faster mounting of symptoms, more or less deceleration of general development, earlier or later onset of social difficulties.

STABILITY OF DIAGNOSIS AND COURSE

The diagnosis of autism spectrum disorder (ASD) made before age 3 has been found to be stable in clinic- and community-ascertained samples, even if with a longitudinal variability for what concern symptoms severity (Chawraska et al. 2007; Chawraska et al. 2009; Guthrie et al. 2013).

As reported by Guthrie et al.: "Improvement of social communication skills, such as joint attention, response to name, and verbal communication, has been reported, although stability

in more global measures of social symptom severity has also been found (Chawarska, Klin, Paul, &Volkmar, 2007)". The model of a continuum of trajectory has been exposed in the previous paragraph. Greater understanding of changes in symptom severity in toddlers would inform studies of diagnostic stability, as changes in symptoms are likely to accompany movement on or off the autism spectrum, but may also be observed in children with stable diagnostic presentations.

In a study published in 2007 Chawarska et al. analyzed the stability of diagnosis in a group of children under the age of two referred to a specialized clinic for a comprehensive multidisciplinary assessment and reassessed at 3 years. The clinical presentation of autism and PDD-NOS in the second year of life and changes in the syndrome expression in a 1- to 2-year period, the relationship between ADOS-G and ADI-R and clinical diagnosis and the relationship between direct clinical observation and parental report of symptoms under the age of two years were also assessed. Stability of diagnosis was high (of the original 21 Autism diagnosis, 19 retained autism diagnosis and 2 met criteria for PDD-NOS; 6 PDD-NOS diagnosis were confirmed). In respect to changes in syndrome expression, relatively to communication the level of language improved in both groups, as did the frequency of communication directed to others, but the latter remained in the pathological range especially in the Autism group (emergence of speech was not accompanied by more frequent and spontaneous use of pointing and only a marginal increase in the use of other communicative gestures); the other key symptoms, except responsivity to joint attention, remained stable: very limited coordination of social- communicative behaviors, eye contact, initiation of joint attention, inability to direct facial expressions to others and limited response to name; together with language also unusual linguistic features, including echolalia and abnormal pitch or intonation began to emerge; in the social interaction scale of ADOS-G limited changes were revealed: an improvement in responsivity to joint attention was noted in both groups; the scores in stereotypic behaviors domain were stable over time. At time 1 in all but one Autism cases there was agreement between clinical diagnosis and the ADOS-G diagnostic classification; the agreement in PDD-NOS children was only of 33%. There were moderate correlations between parental report and clinician's impression in Communication and Social Reciprocal interaction, but not in the Stereotyped Behaviors domains. In the second year of life limited response to name, poor eye contact, limited response to joint attention bids, lack of pointing and delays in functional and symbolic play were found. Differences between Autism and PDD-NOS at both time points were pronounced and stable.

In Guthrie et al. (2013)results indicated that significant changes in symptom severity were observed even when diagnosis was stable, suggesting that the toddler years are marked by changes in global symptom severity; although children with and without ASD differed on symptom severity at initial evaluation, improvement in social communication and interaction was observed at similar rates across diagnostic groups; in contrast, restricted and repetitive behaviors increased (i.e., worsened) in children with ASD, while they remained stable in children without ASD.

In a recent paper (Ozonoff et al., 2015; ahead of print) the diagnostic stability of high risk infants has been examined in a large (418) multicenter sample of siblings evaluated at 18, 24 and 36 months of age. The findings report the stability of an ASD diagnosis at 18 months of 93% and at 24 months of 82%; there relatively few children diagnosed with ASD at 18 or 24 months whose diagnosis was not confirmed at 36 months. There were, however, many children with ASD outcomes at 36 months who had not yet been diagnosed at 18 months (63%) or 24 months (41%).Thus, based on the data, the Authors suggest that: longitudinal follow-up is critical for children with early signs of social-communication difficulties, even if they do not meet diagnostic criteria at initial assessment; screening for ASD may need to be repeated multiple times in the first years of life; there is a period of early development in which ASD features unfold and emerge but have not yet reached levels supportive of a diagnosis.

Chapter 2.2

EARLY DETECTION: FIRST AND SECOND LEVELS OF INVESTIGATION

Despite the increasing knowledge of early signs and the recognition of the utility of early diagnosis, early detection and diagnosis still are challenges.

In order to reduce the gap between parents' first concern and confirmation of diagnosis, clinical practice guideline (Filipek et al., 2000; Johnson et al., 2007) and reviews have been published (Charman & Baird, 2002; Falkmer et al., 2013). However there is still a great heterogeneity of screening and diagnostic procedures both between different countries and within the same country (Garcia Primo, 2014).

In their work Filipek et al. (2000) report that the clinical identification of children with ASD requires two levels of investigation. The first level, Routine Developmental Surveillance and Screening Specifically for Autism, that involves first identifying those children at risk for any type of atypical development, followed by identifying those specifically at risk for autism; a

second level, Diagnosis and Evaluation of Autism, involves a more in-depth investigation of already identified children and differentiates autism from other developmental disorders.
Due to the heterogeneity of symptoms and onset the recommendation is to screen for ASD at the 18 and at the 24 months (Johnson et al., 2007, Zwaigenbaum et al., 2009).

Level 2 of investigation

As reported in Charman and Baird (2002) a multidisciplinary approach to diagnostic assessment is required. The composition of teams varies across centers, but commonly includes a child psychiatrist, a speech and languagetherapist, a clinical psychologist and an occupational therapist or physiotherapist. The comprehensive evaluation has to include: a detailed developmental history, parents' descriptions of the everyday behaviour and activities of the child; direct assessment of the child's social interaction style when possible also with age peers at nursery or pre-school; language and communicative evaluation; cognitive and adaptive function evaluation, academic assessment and, eventually, integration with neuropsychological evalutaion; behavioral and educational evaluation; eventual integration with a sensory-motor(/occupational therapist) evaluation (gross and fine motor skills, praxis, sensory processing abilities) to detect specific patterns of sensory integrative dysfunction.
The assessment process is supported by the use of assessment tools. In a recent review (Falkmer et al., 2013) ADI-R and ADOS have been confirmed as the 'gold standard' tools for diagnosis of ASD; however, the true 'gold standard' classification and diagnosis of autism is still confirmed to be multi-disciplinary team clinical assessment, including use of the ADOS and ADI-R, as well as other assessments with consensus clinical judgment. Recently (since 2012) a new module of ADOS addressed to Toddler (ADOS-T, designed for children under the age of 30 months who have non-verbal mental ages of at least 12 months and motor skills that allow them to at least cruise their environment) is available. Scores on the ADOS-T fall into categories reflecting overall level of concern regarding the likelihood that the child has ASD: little or no concern, mild or moderate, moderate or severe. The ADOS-T demonstrated very good sensitivity and specificity in the validation sample (Luyster et al. 2009).
Other tools used by the clinicians in the ASD assessment exists (i.e. Autism Observation Scale for Infants (AOSI, Bryson et al. 2007), Childhood Rating Scale (CARS, Schopler1986), Autistic behavioral indicators instrument (ABII, Bornstein 2010), Diagnostic interview for social and communication disorders (DISCO, Leekam 2002); Screening Tool for Autism in Two-Year-Olds (STAT, Stone 2000).

Medical investigations are needed to complete the assessment process: a general physical and neurological examination, biochemistry and metabolic tests as per mental retardation protocols; genetic analysis (high resolution kariotype/array-CGH and fragile X analysis) and eventually genetic evaluation, sleep EEG is recommended in children who have a history of loss of functions; neuroimaging is not routinely recommended in autism unless there are other neurological indications. Further investigations are required if a child has a fluctuating clinical course or additional features.

The overall assessment process is meant to confirm/not confirm a diagnosis of ASD, evaluate possible differential diagnosis, assess the overall development domains (in particular developmental level and language) and co-occurring symptoms, identify possible associated or causative medical conditions.

The diagnostic process results long and time consuming and requests personnel trained in the use of the specific diagnostic tools.

Some parents rated tools have been developed in order to support the clinical assessment. They present the advantages to be less time consuming and to constitute a manner to recollect and evaluate objectively parents information (normative data).

Within the level 2 parent rated measure are comprised instruments as like the Baby and Infant Screen for Children with Autism Traits (BISCUIT, Matson 2009), the Developmental Behaviour Checklist-primary care version (DBC-ES, Gray 2005) (see Garcia-Primo et al., 2014 for a comprehensive report).

In synthesis actually an ASD evaluation should include, at minimum, a caregiver-based developmental history, a direct observation of the referred individual using a semi-structured observational measure, and measures of cognitive, language, and adaptive skill; despite the strong predictive validity of some of the assessment tools described above, an individual's diagnosis of ASD should never depend on the diagnostic classification of a single measure or combination of measures.

Level 1 instruments are described in Chapter 3

Chapter 3

Screening tools: specific and broadband tools

The first level investigation (Routine Developmental Surveillance and Screening Specifically for Autism) involves first identifying those children at risk for any type of atypical development, followed by identifying those specifically at risk for autism (Filipek et al. 2000) in order to address those children found to be at risk of ASD toward a second level evaluation. Actually many instruments have been developed and/or are in course of study with the scope of ASD screening. However there is still a great heterogeneity in screening programs (Garcia-Primo et al., 2014) and the "gold standard" of screening tool is not yet been established.

The efficacy and utility of screening instruments is based on several parameters, within which the sensitivity, the specificity and the positive predictive value. As reported in Charman & Gotham (2013): Sensitivity is required to be high in order that the screen misses few cases of the disorder (avoiding falsely reassuring parents and professionals); specificity is required to be high in order that few cases without the disorder are screen positive (avoiding falsely alarming parents and costly referral for in-depth); the positive predictive values is lower the rarer a disorder is within the population, hence, PPV will be lower in population than in referred samples. Glascoe (2005) has estimated that acceptable sensitivity and specificity for developmental screening tests are 70% to 80%.

Many first level instruments have been developed in the last years. This confirms the knowledge of their crucial role in screening and diagnosis, however for many of the available tools the validity as screening measures is limited by the limited research on their use. In many cases, sensitivity and specificity of the instruments have been determined only in clinical samples or in populations that included a mixture of clinical and population-based samples, and they must be interpreted with caution.

Even when the study has been designed in a community population one of the major limitation of level 1 screening research is the impossibility to evaluate all negative cases (problem of the false negative cases) and the consequent impossibility to calculate the true sensitivity; an additional challenge is the drop-out of screened positive. (Robins et al., 2014)

In Matson, Rieske, et al. (2011); Charman& Gotham (2013); Garcia Primo et al. (2014) are reported reviews of the available screening and diagnostic tools.

Within the first level instruments we can recognize two typologies of instruments: the **ASD-specific tools** and the **broadband tools**.

Chapter 3.1

ASD-SPECIFIC TOOLS

Within the ASD-specific tools, the most popular and diffusely used are the CHAT and MCHAT.

The CHAT is the first instrument thought to be a screener for ASD (Baron-Cohen et al., 1992); CHAT was developed to identify autism based on parents' reports of child behavior and semi-structured observation of child behavior by a health practitioner, at 18 months of age. It consists of 14 questions, divided into two sections: section A comprises nine questions which are answered by parents; section B consists of five questions which are observed by a health practitioner .This is also the unique instrument that has been studied in a large first level sample with data of follow-up for both screen-positive and screen-negative (Baird et al. 2000) . In that study CHAT has demonstrated an excellent specificity (1.00-0.98), but a sensitivity of(0.21-0.38) and a positive predictive value (PPV) of 0.26-0.05 (for a high-risk screen a medium risk screen respectively).

The same research group is developing a revised version, the Quantitative-Checklist for Autism in Toddlers (Q-CHAT: 25 items, scored on a 5 point scale) thought to improve the sensitivity (Allison et al., 2008).

The modified form of the CHAT (M-CHAT), is a 23 items parent questionnaire, the observation section has been eliminated; it is directed to a wider age range population (18-30 months) than the CHAT. In their initial report, Robins et al. (2001) had tested 1.122 unselected children (at 18 and 24 months of age) and 171 children referred for early intervention services (considered to be at high risk of having an ASD or other developmental disability). Once a child failed the M-CHAT the research team re-administered the screen by telephone, and if a child still scored above cut-off the family was invited for an assessment.

Of the 58 children who failed on both administrations of the M-CHAT, 39 subsequently received an ASD diagnosis and the remaining 19 were found to have language or global developmental delay. Robins et al. (2001) calculated sensitivity, specificity and PPV for

various combinations of M-CHAT items and demonstrated that in this largely referred sample its instrument parameters were reasonably strong (PPV for 2-stage 63%).

In a second study (Kleinman et al., 2008), the MCHAT was applied in a mixed sample(children aged 16-30 months from low- and high-risk sources) with a subset group receiving follow-up around four year of age. Kleinman and colleagues (2008) found a PPV of 0.36 for the initial screening, which improved to 0.74 for the screening plus the follow-up telephone interview. In both the studies high values of false positive were found and the phone interview was necessary to increase the Positive predictive value. Subsequently MCHAT has been used in an exclusive level 1 sample at 18- and 24-months ages (Robins 2008) finding a moderate level of PPV for the M–CHAT plus follow-up interview (0.57).

Sunita and Bilstza (2013) have reviewed the literature evidence for screening for autistic symptoms in very young children using CHAT and M-CHAT. Based on their findings M-CHAT has demonstrated slightly better sensitivity and specificity compared to CHAT; however the calculation of M-CHAT psychometric properties is biased by the use of combined participants from unselected and early intervention population groups (except for Robins et al. 2008); another reported area of concern is constituted by the high false-positive rates, particularly when used without interview. To overcome these limitations, longitudinal studies are required to accurately calculate sensitivity and specificity scores.

In a recent study (Robins, 2014) the revised form of MCHAT plus follow up has demonstrated to be an effective tool for screening low-risk toddlers, reducing the age of diagnosis by 2 years (Children whose total score was ≥3 initially and ≥ 2after follow-up had a 47.5% risk of being diagnosed with autism spectrum disorder (ASD; confidence interval [95% CI]: 0.41–0.54) and a 94.6% risk of any developmental delay or concern (95% CI: 0.92–0.98); the sensitivity and specificity reported for this algorithm are 0.85 and 0.99 respectively .

Within the many other first level instruments which have been developed in the last years there are: the First Year Inventory(FYI) (Reznick et al., 2007); the Early Screening of Autistic Traits Questionnaire (ESAT) is an empirically based screening instrument for use in high-risk populations; it consists of 14 easy to-administer items measuring early social-communication skills, play, and restricted and repetitive behaviors, answered with yes or no (Dietz et al., 2006; Swinkels et al., 2006; Oosterling et al. 2009; Oosterling et al., 2010).

Chapter 3.2

BROADBAND TOOLS

Broadband tools exit for the developmental and behavioral screening at different ages (see Glascoe, 2005 for a review). In a two steps screening model (Filipek et al., 2000) the first level of investigation involves first identifying those at risk for any type of atypical development (Routine Developmental Surveillance) followed by identifying those specifically at risk for autism (Screening Specifically for Autism). In the AAP policy, "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (AAP, 2006), a general developmental screen is recommended at the 9-, 18-, and 24-or 30-month visits and an ASD screening is recommended at the 18-month visit; the report of AAP "Identification and Evaluation of Children With Autism Spectrum Disorders" (Johnson & Myers, 2007) also recommends an ASD screening at the 24-month visit to identify children who may regress after 18 months of age, should be performed on all children.

Some broadband tools have been suggested for the identification of ASD. The broadband instruments are already largely used in clinical practice. Their use as ASD screener could contemporary screen for a broad range of problems and evaluate the risk of ASD without the necessity of someone to formulate the suspicious of ASD. Dumont-Mathieu & Fein (2005) for example, report the Parents' Evaluation of Developmental Status (PEDS), the Ages and Stages Questionnaire (ASQ Bricker and Squires, 1999), and the Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP, Wetherby and Prizant, 2002) suggesting that, even if those instruments are not designed to selectively screen for autism, they may be effective in detecting children whose developmental problems are consistent with autism.

The CSBS DP(CSBS DP, Wetherby and Prizant, 2002) is a screening and evaluation instrument designed to measure the communicative and symbolic abilities of children aged 12–24 months. The measured skills form three composites: social (emotion, eye gaze, and communication), speech (sounds and words), and symbolic (understanding and object use). The Communication and Symbolic Behavior Scales Developmental Profile includes three measures: the Infant-Toddler checklist, an expanded Caregiver Questionnaire, and a Behavior Sample (video). Wetherby et al., (2004) propose the use of the Infant-Toddler Checklist as a first level screen, with the Behavior Sample serving as a second level evaluation tool.

Within the broadband instruments one of the mostly used is CBCL (Achenbach & Rescorla, 2000). Different studies have provided support for the CBCL in identifying subjects with ASD at different ages. Bolte et al. (1999)found that children and adolescents (4–18 years) with autism showed higher scores on the CBCL scales measuring attention problems, social problems and thought problems, and lower scores on the scale for somatic complaints. Duarte et al. (2003), using the CBCL 4–18 in school aged children, found a CBCL factor called Autistic/Bizarre that was able to differentiate autistic conditions from Other Psychiatric Disorders (with a sensitivity of 0.89 and a specificity of 0.80)and from typical schoolchildren (with a sensitivity of 0.94 and a specificity of 0.94). Biederman et al. (2010) evaluated the properties of CBCL in discriminating referred children with ASD from psychiatrically referred children without ASD. Their study showed that the Withdrawn, Social Problems, and Thought Problems scores were the best independent predictors of ASD conditions. In their study, Receiver Operating Characteristic (ROC) analyses showed that Withdrawn + Social + Thought Problems scores yielded an area under the curve of 0.86, indicating an 86% chance that a randomly selected sample of children with ASD will have abnormal scores on these scales. These findings suggested that a new CBCL-ASD profile consisting of the Withdrawn, Social, and Thought Problems scales could serve as a rapid and cost-effective screening instrument to identify school aged children likely to meet criteria for ASD in the clinical setting. Ooi et al. (2011) tested the ability of the CBCL to discriminate among children with ASD, children with Attention Deficit and Hyperactivity Disorder (ADHD), clinicallyreferred children who did not receive a diagnosis, and typically developing (TD) children. Ooi et al. (2011) showed that Withdrawn, Social Problems, and Thought Problems scales significantly discriminated the ASD sample from other groups. In their study, an ASD cluster composed of nine CBCL items demonstrated moderate to high sensitivity (0.68–0.78) and specificity (0.73–0.92). All these studies provide strong support for the CBCL as a screening tool for older children with ASD.

The recent CBCL form for preschoolers (Achenbach &Rescorla, 2000) has identified a specific DSM Oriented scale named Pervasive Developmental Problems (PDP), which is supposed to be useful in identifying children under the age of 6 at risk for ASD. Two studies have shown a good predictive validity of the PDP scale (with both sensitivity and specificity above 0.80) in identifying preschoolers with an ASD diagnosis (Sikora et al., 2008; Muratori et al., 2011).

We have recently analyzed the utility of the CBCL ½-5 as ASD detection tool in younger children (12-36 months) :

Child Behavior Check List 1½–5 as a tool to identify toddlers with Autism Spectrum Disorders: A case-control study

Antonio Narzisi, Sara Calderoni, Sandra Maestro, Simona Calugi, Emanuela Mottes, Filippo Muratori

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In this paper we have evaluated the sensitivity and specificity of the Child Behavior Check List 1½–5(CBCL 1½–5) in the detection of toddlers subsequently diagnosed with an Autism Spectrum Disorder (ASD), aged 18–36 months. The CBCL of 47 children with ASD were compared to the CBCL of 47 toddlers with Other Psychiatric Disorders (OPD) as well as to the CBCL of 47 toddlers with Typical Development (TD) in a case control study. One-way analysis of variance (ANOVA) and logistic regression with odds ratio (OR) analyses were performed. In order to establish the optimal threshold able to discriminate children with ASD from children with OPD and TD, Receiver Operating Characteristic (ROC) analyses were performed. One-way ANOVA revealed significant differences between the three groups. Logistic regression analysis showed that the Withdrawn and the Pervasive Developmental Problems (PDP) subscales can recognize toddlers subsequently identified as ASD from both children with TD ($p < 0.001$) and OPD ($p < 0.001$). ROC analyses showed very high sensitivity and specificity for the PDP (0.98 and 0.91) and Withdrawn (0.92 and0.97) subscales when ASD was compared to TD. Sensitivity and specificity of Withdrawn (0.90 and 0.83) and PDP (0.85 and 0.83) remained high when comparing ASD versus OPD. In conclusion, the CBCL 1½–5 seemed to be able to identify toddlers subsequently diagnosed with ASD from children with TD and OPD. Its high sensitivity and specificity, coupled with its efficiency in terms of time and cost, suggest this broadband tool should be tested in a pilot screening survey of toddlers in the general population.

Myers et al. (2014)The purpose of their research was to determine if any of the scales on the Child Behavior Checklist for ages 18 months–5 years,11 months (CBCL/1.5-5, Achenbach and Rescorla2000), Behavior Assessment System for Children, second edition (BASC-2, Reynolds and Kamphaus 2004), The Clinical Assessment of Behavior (CAB, Bracken and Keith 2004) could differentiate between young children with ASD (mean age 40,2 months) and other clinically referred, but non-ASD children (mean age 32,8 months). The results found four scales from two instruments (BASC-PRS-P Social skills and Functional

communication scales; CBCL ½-5 Withdrawn and PDP scales) that resulted in mean scores outside the average range and had statistically significant differences; however the Authors concluded that the small mean score differences and analyses of sensitivity and specificity suggested that those scales have limited practical usefulness when used by clinicians.
A literature review concerning the application of ITSEA and BITSEA in the ASD population is reported in Chapter 4.

In the table are reported some studies concerning some of the available parent-rated first level tools (S.P., screening population (general population; samples could include low and high risk children); G.C., group control (ASD already diagnosed versus other developmental problems and/or typical groups); mo, months; Se., sensitivity; Sp., specificity).

AUTHORS	TOOL	TYPE OF STUDY	SAMPLE	AGE	PSYCHOMETRIC VALUES
Baird et al. (2000)	CHAT	S.P. (unselected)	n=16.235	17-20 mo	Se .21-.38 Sp 1.00-.98
Robins et al. (2001)	MCHAT/F	S.P. (unselected and high risk)	n=1293	18-24 mo	Se.87 Sp .98
Robins et al. (2014)	MCHAT-R/F	S.P (unselected)	n=16.115	18-24 mo	Se .85 Sp .99
Watson et al. (2007)	FYI	G.C	n=38	14-75 mo	Se .71-.92 Sp 1.00-.79
Oosterling et al. (2009)	ESAT	S.P. (selected high risk)	n=238	8-44 mo	Se .88 Sp .14
Wheterby et al. (2004)	CSBS-DP Infant-Toddler Checklist	(G.C.)	n=54	18-21 mo	Se .89 Sp .89

Chapter 4

The Infant-Toddler Social and Emotional Assessment (ITSEA)

This chapter is comprised of two parts: a first part in which the tool object of study, the Infant-Toddler Social and Emotional Assessment (ITSEA), is described; the second part is constituted of a review of the studies in which ITSEA has been used in ASD population. Information about the brief version of ITSEA (Brief Infant-Toddler Social and Emotional Assessment) are reported too.

Chapter 4.1

ITSEA and BITSEA description

ITSEA

ITSEA is a parent-report measure of social and emotional development in children age 12 to 36 months. It is comprised of 169 items rated on a 3-point scale (not true/rarely, somewhat true/sometimes, very true/often); a childcare-report form is also available; the completion requires approximately 30 minutes.

The growing awareness of the presence of mental health problems in early childhood (Briggs-Gowan et al. 2001; Carter et al. 2004; Egger and Angold 2006); the need of age-adequate tools to study their prevalence (Briggs-Gowan et al. 2001) and their course (Briggs-Gowan et al. 2006) and to promote their identification, comprehensive assessment and treatment (Carter et al. 2004) are the basis on which ITSEA was thought and developed. Indeed ITSEA, and its brief version (BITSEA), were developed as developmentally sensitive tools to measure social-emotional and behavioral problems in children aged 12-36 months (Briggs-Gowan& Carter, 1998; Carter et al., 2003; Carter and Briggs-Gowan, 2006).

The original development of the questionnaire was based on the reviews of developmental psychology and psychopathology literature, of the Diagnostic and Statistical Manual-IV-TR (DSM-IV-TR; American Psychiatric Association, 2000), the Diagnostic Classification: 0-3 (DC: 0-3; Zero to Three, National Center for Infant, Toddlers, and Families, 1994) and of the existing instruments for older children. This work resulted in the identification of three broad

domains of problems (Externalizing, Internalizing, Dysregulation) and one domain of Competence; multiple subscales are included within each domain.

Two types of problem behaviors are included: behaviors that occur as part of the typical development, but that can be problematic due to their intensity or frequency; behaviors that are never developmentally appropriate.

The Internalizing domain is intended to capture symptoms of anxiety and depression, as well as more temperamentally based difficulties with inhibition to novelty. The Externalizing domain is designed to address behaviors that may be early manifestations of disruptive behavior disorders and thus includes over activity, aggression, and defiance. The Dysregulation domain was developed to provide coverage of symptoms addressing eating and sleeping problems, negative emotionality, and sensory activities, providing coverage of symptoms included in the criteria for regulatory disorders in the DC: 0–3, such as sleep and feeding disorders and regulatory disorders involving problems in mood regulation.

Two subscales (Inhibition to Novelty, within the Internalizing Domain, and Negative Emotionality, within the Dysregulation Domain) reflect temperamental aspects.

The Competence domain enables to assess possible delay in the acquisition of chronological or mental-age appropriate social and emotional competencies and to identifying areas of strengths. The choice to include the assessment of the social emotional competencies was based on the belief, and on the subsequent literature demonstrations, that delays in acquiring social-emotional abilities may be a risk factor for the acquisition of new developmental demands and for social and emotional problems.

The profile also includes three Item Clusters (Maladaptive, Social Relatedness and Atypical Item Cluster) which address infrequent behaviors referring to specific psychopathological conditions; in particular the Social Relatedness and the Atypical Item Clusters refer to the Autism Spectrum symptoms.

The items proposed were collaboratively developed by the Authors, retained in case of consensus and then reviewed by a team of developmental psychologists and child psychiatrist experts in social-emotional development and psychopathology in early childhood.

To minimize response set biases, problem and competence items are interwoven throughout the ITSEA.

An example of the ITSEA summary profile with domains and subscales is reported in Figure 1, at the end of the chapter.

The reliability and validity of the ITSEA and of the BITSEA, have been examined in several prior studies (Briggs-Gowan & Carter, 1998; Carter et al., 1999; Carter et al., 2003; Briggs-Gowan et al., 2004; Briggs-Gowan & Carter, 2006; Carter & Briggs-Gowan, 2006).

In a first pilot study the items were tested with parents of clinic referred-children and revised for readability and response format (Briggs-Gowan& Carter, 1998). In a second phase of development ITSEA was tested in a small non referred sample of children from a socio-demographically diverse pediatric sample (Briggs-Gowan& Carter, 1998), demonstrating acceptable internal consistency and test-retest reliability, as well as validity when compared with results on parent-report measures of parenting stress and problem behaviors. In another study, which focused on a sample of 12-month-olds, ITSEA demonstrated significant association with observational measures of social-emotional functioning, such as attachment security, mastery motivation, and emotion regulation (Carter et al., 1999).

In 2003 the reliability and validity of ITSEA were evaluated in a representative, sociodemographically diverse birth cohort sample of 1235 children. The validity of the internal structure was tested through a confirmatory factor analysis followed by the analysis of the appropriateness of the domains and scales for both boys and girls across four age bands (12-17; 18-23; 24-29; 30-35 months); the degree of construct independence was examined through the analysis of intercorrelations between the resulting domains and scales; criterion validity was evaluated through the analysis of the association between ITSEA and other measures of the same construct. Traditional psychometric properties were evaluated too: coefficient alpha (internal consistency) ranged from .45 to .90; test-retest reliability and inter-rater reliability were tested in a subset of families (ICC from .69 to .90 and from .43 to .79 respectively). The analysis of subgroups defined by age and sex showed higher means for girls on Compliance, Attention, Imitation/Play, Empathy, Prosocial peer relation; all competence's scores increased across age groups; there were no gender or age effects for the three clinical item clusters; Activity, Eating problems and Separation Distress scores appeared to diminish across the age bands; while General Anxiety and Depression/Withdrawal appeared to increase with age.

ITSEA has been standardized and normed based on a nationally representative sample(Carter & Briggs-Gowan, 2006). The normative sample was comprised of 600 children aged 12 to 35 months 30 days, and was designed to represent the four age bands and gender, given the previous findings relative to age and sex differences. Each of the four Domains have been converted to age (4 bandages)- and sex-specific T scores that have a normalized mean of 50 and a standard deviation of 10. A T score of of/above 65 in the Problem Domains and

of/below 35 in Competence Domain is considered "of concern". Age and sex specific cutpoints to indicate "of concern" scores have been established for scales and item clusters, too; the cutpoints indicate scores that are in the top 10% of problems or lowest 10% of competence scores in the normative population.

The analysis in the normative sample have confirmed the increase of competencies across age bands for both male and females, and higher mean scores for female in the Competence Domain, in the Attention, Imitation/Play and Prosocial Peer Relations scales. Males have shown a higher mean score in the Activity/Impulsivity scale. Differences in General Anxiety across age bands are present both for girls and boys with a trend characterized by increases in scores across the first three age bands.

In the normative population the ITSEA subscales and domain have established acceptable internal consistency (Cronbach's alphas from .52 to .90); test-retest reliability and inter-rater agreement have been evaluated using the Intraclass Correlation Coefficient (ICCs in the overall group from .64 to 90 and from .44 to .83, respectively). In the normative sample, validity has been also established on the basis of the study of correlation within domains and scales (correlation between subscales and their respective domains moderate to strong; the low association between Problem Domains and the Competence domains gives evidence of divergent validity in the measuring of problems and competencies as separate construct) and relative to observational measures and other parent-report checklists (Child Behavior checklist (CBCL ½-5, Achenbach &Rescorla, 2000); Ages and Stages Social-emotional Questionnaires: Social emotional (ASQ-SE; Squires et al., 2002); the Adaptive behavior Assessment System: Second Edition (ABAS-II, Harrison & Oakland, 2003); Bayley scales of Infant and Toddler Development-Third Edition (Bayley-III, Bayley, 2006)).

In a section of ITSEA Manual, the validity of the instrument is also supported by the examination of ITSEA profiles across clinical groups that are expected to differ in term of social-emotional and behavior problems profiles. The groups object of analysis are: a Developmental Delay sample (n= 93; m=56.99 %, f=43.01 %; age range 12-35 months); an Autistic Disorder sample (n=33; m=72.73 %, f=27.27 %; age range 18-35 months); a Mental Health Disorder sample (n=22; m=50.00 %, f=50.00 %; age range 12-35 months); a Language Delayed sample (n=56; m=37.50 %, f=62.50 %; age range 12-35 months); a Premature birth sample (n=56; m=54.35 %, f=45.65 %; age range 12-35 months).

The Developmental Delay sample showed, in the comparison with a typical development control group, significantly lower score in the Competence Domain with the larger effect

sizes for the overall Competence Domain and the Mastery Motivation and Imitation/Play subscales; the Development Delay sample also showed higher scores in the Social Relatedness and Atypical item clusters.

The Autistic Disorder sample consisted of children referred to the research study primarily from early intervention clinics; the diagnosis was determined based on clinical evaluation and on meeting criteria for Autistic Disorder on both ADOS (Lord et al. 2000) and ADI (Lord et al. 1994); children with pervasive developmental delay not otherwise specified (PDD-NOS, DSM-IV) were not included in the sample.

The Autistic Disorder group was expected by the Authors (Carter & Briggs-Gowan, ITSEA Examiner's Manual, 2006) to show a specific profile with deficits in the ITSEA Competence domain and subscale scores and elevated ITSEA Dysregulation domain and subscales scores. At the subscale level elevated scores were expected in the Depression/Withdrawal subscale (Internalizing Domain), in the Eating and Sensory Sensitivity subscales (Dysregulation Domain); the Social Relatedness and Atypical Item clusters, which measure core symptoms of Autistic Disorders, were also expected to differ between groups. The results of the comparison with a matched control group confirmed what expected finding significant and strong (large effect size) differences in the Competence Domain and subscales, in the Social Relatedness and Atypical Items Cluster and in the Depression/Withdrawal subscale (Internalizing Domain). Additional significant differences were found in the Activity/Impulsivity subscale (Externalizing Domain), in the Dysregulation Domain(Eating subscale followed by Negative Emotionality subscale and Sensory Sensitivity subscale and in the Maladaptive item cluster.

Data regarding the comparison between a sample with Autistic Disorder (n=22), a sample with Developmental Delay (n=22) and a sample with Typical Development (n=22), matched for nonverbal developmental test scores, are also reported in the Manual(unpublished data). The results confirmed differences in the Social Relatedness and Atypical Item clusters, in the Depression/Withdrawal, in the Dysregulation Domain and its Eating and Negative Emotionality subscales and in the overall Competence Domain and several competence subscales with the strongest effect in the Imitation/Play, Mastery Motivation, Empathy and Prosocial Peer Relations subscales; higher scores in the General Anxiety and Sleep subscales are also reported in the comparison with the Typical Development sample. Within the Problems scales the largest effect size was found for the Depression/Withdrawal scale.

In the Mental Health Group are comprised children meeting criteria for a psychiatric diagnosis using DSM-IV and/or CD: 0-3 classification systems; diagnoses were assigned after

a comprehensive psychiatric interview, chart review, observation of children interacting with their primary caregiver in two situations (structured and free play) and observation during a standardized developmental assessment; the range of psychiatric disorders comprised externalizing disorders (e.g. Oppositional Defiant and Attention Deficit and Hyperactivity Disorders); internalizing disorders (e.g. Separation Anxiety, Social Anxiety Disorders); DC: 0-3 Regulatory Disorders. Some children were assigned more than one diagnosis, some had language delays, children with Autism spectrum disorder were excluded. In the comparison with a typical development matched control group, what expected were higher scores in all Problems Domain and deficits in the Competence Domain, even if not all statistically significant because of the small sample size. The results of the mean scores comparison show large effect sizes in the Problem and Competence Domains. Particularly large effect size were observed for the Aggression/Defiance subscale (Externalizing Domain; no statistically significant difference), Separation Distress subscale (Internalizing Domain), Negative Emotionality and Eating subscales (Dysregulation Domain); all of the Competence subscales except for Empathy. The Atypical Item cluster score also resulted statistically different ($p < .01$).

BITSEA

BITSEA is comprises of 42 items that are drawn from the longer ITSEA and that are divided into a 31-item Problem Scale and an 11-item Competence Scale; the response format is a 3-point scale; 5 to 7 minutes are requested for the completion. The BITSEA screener was first developed in the birth cohort sample of 1235 children(Briggs-Gowan et al., 2004) and it has been standardized and normed based on a nationally representative sample (Briggs-Gowan& Carter, 2006). As like ITSEA, different cutpoints are available for gender and age-bands. BITSEA screening cutpoints are designed to broadly capture children with potential problems that merit additional follow-up and/or assessment. The Problem cutpoint is designed to identify children with scores at or above the 75th percentile in the normative birth cohort; the Competence cutpoint is designed to identify children with scores in the lowest 10th–15th percentile relative to the birth cohort.

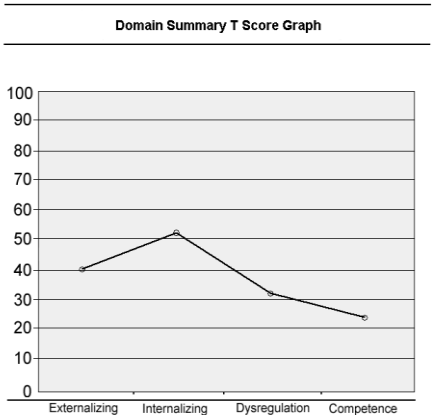
In the sample study (Briggs-Gowan et al., 2004) it has demonstrated moderately acceptable internal consistency Cronbach's =.79 for Problems and .65 for Competence; according to the Manual the test-retest reliability is good-to-excellent (r .92 for the Problem Total score and .82 for the Competence Total score) and the inter-rater agreement is good (ICC from.70 to .78 for girls for the Problem Total score; .58 for girls and .67 for boys for the Competence Total score).

Similar to the findings for the ITSEA, BITSEA Problem scale and Competence scales have demonstrated validity relative to parental reports of problems on other standardized measures(Child Behavior checklist (CBCL ½-5, Achenbach &Rescorla, 2000); Ages and Stages Social-emotional Questionnaires: Social emotional (ASQ-SE; Squires et al., 2002); the Adaptive behavior Assessment System: Second Edition (ABAS-II, Harrison & Oakland, 2003); Bayley scales of Infant and Toddler Development-Third Edition (Bayley-III, Bayley, 2006)), as well as in relation to special groups studies (a Developmental Delay sample; an Autistic Disorder sample; a Mental Health Disorder sample; a Language Delayed sample); a Premature birth sample) (Briggs-Gowan et al., 2004; Briggs-Gowan& Carter, 2006).

Figure 1. ITSEA: summary profile

Subscale Scores Summary

Subscale	Raw Score	Cut Point	Status of Concern	Percentile Rank
Externalizing Domain				
Activity/Impulsivity	0.33	1.35		>=90
Aggression/Defiance	0.36	0.81		60-69
Peer Aggression	0.17	0.77		60-69
Internalizing Domain				
Depression/Withdrawal	0.44	0.39	Of Concern	5-9
General Anxiety	0.00	0.59		>=90
Separation Distress	1.00	1.3		30-34
Inhibition to Novelty	0.75	1.57		50-59
Dysregulation Domain				
Negative Emotionality	0.15	0.99		>=90
Sleep	0.20	1.14		70-79
Eating	0.44	0.96		40-49
Sensory Sensitivity	0.29	0.85		60-69
Competence Domain				
Compliance	1.25	0.91		35-39
Attention	0.80	0.95	Of Concern	5-9
Mastery Motivation	1.00	1.18	Of Concern	1-4
Imitation/Play	0.50	0.88	Of Concern	<1
Empathy	1.00	0.84		15-19
Prosocial Peer Relations	0.60	0.7	Of Concern	5-9
	Item	**Cluster**		
Maladaptive Item Cluster	0.15	0.2		
Social Relatedness Item Cluster	1.50	1.27		
Atypical Item Cluster	0.63	0.61	Of Concern	



Domain	Raw Score	T Score	Cumulative %	Status Of Concern	# of Subscales "Of Concern"
Externalizing	0.29	40	90.00		0
Internalizing	0.55	52	41.30		1
Dysregulation	0.27	32	100.00		0
Competence	0.86	25	1.70	Of Concern	4

Chapter 4.2

4.2.1 ITSEA and BITSEA in ASD literature

For both ITSEA and BITSEA data about application in group of children with a diagnosis of Autism Disorder (n=33) are reported in the manuals.

The findings concerning the ITSEA have been discussed above.

For what concern BITSEA, significant differences in the comparison with a matched control group were found for both the Problem and the Competence scores: The sensitivity-specificity analysis showed excellent sensitivity and specificity for the Competence score (Se 100%, Sp 90.1 % considering the cut score at the 15th percentile of the normative population); with the Problem scores, 97% of normally developing children were identified as normally developing (Specificity) whereas 63.3% of children with autism were correctly identified as having Autistic Disorder (Specificity), considering the cut off at the 25th percentile.

We made a literature review of the studies that have used ITSEA and BITSEA in the ASD population.

To our knowledge previous literature data concerning the analysis of the ITSEA profile in ASD and its capacity to distinguish between different clinical conditions are referred to smaller samples of ASD (Carter et al., 2004 (unpublished data); Carter and Briggs-Gowan, 2006; Visser et al. 2007). In other studies ITSEA has been used as measure of social-emotional development, but they are not primarily aimed to the identification of an ITSEA profile indicative of ASD. The studies reviewed are summarized in table 1 and 2

Table 1 ITSEA in ASD population

Study (Design)	Groups (mean age±SD; range)	Main aims	Measures	Results regarding ITSEA
Carter et al. 2007 (Observational cross-sectional)	ASD: n= 90 m: 75,6 %, f: 24,4 % (28,1±3,9; 20-33)	Sex differences with respect to profiles of developmental functioning	VABS (Sparrow et. al., 1984) ITSEA (Carter & Briggs-Gowan, 2006) ADI-R (Lord et al., 1994) ADOS-G (Lord et al., 2002) Mullen Scales of Early Learning (Mullen, 1995)	Female lower scores on Competence domain, Empathy and Mastery motivation scales; trends towards lower female score in Social relatedness and higher scores in Depression/Withdrawal and Atypical items cluster
Ben-Sasson et al. 2007	ASD: n= 100 m: 76 %, f: 24 %	Incidence of extreme	ITSP (Dunn, 2002)	ITSEA Sensitivity scale:

(Observational case-control; ASD sample: same cohort of Carter et al.2007)	(27,92±4,01; 18-33) CA matched: n= 100 m: 76 %, f: 24 % (27,57±3,93; 20-33) MA matched: n= 99 m: 74, 7 %, f: 25,3 % (17,57±5,76, 7-35)	sensory modulation in ASD toddlers Consistency of sensory information across measures	ITSEA (Carter & Briggs-Gowan, 2006) Sensory Sensitivity Scale ADI-R (Lord et al., 1994) ADOS-G (Lord et al., 2002) Mullen Scales of Early Learning (Mullen, 1995)	negative correlation with ITSP Low registration, Avoiding Sensitivity ; positive correlation with ADI-R Noise Sensitivity and Unusual negative sensitivity
Davis – Carter 2008 (Observational cross-sectional; same cohort of Carter et al.2007)	ASD: n=54 m: 74,1 %, f: 25,9% (26,9±4,2)	Parenting stress in young newly ASD diagnosed children	ADI-R (Lord et al., 1994) ADOS-G (Lord et al., 2002) Mullen Scales of Early Learning (Mullen, 1995) ITSEA (Carter & Briggs-Gowan, 2006) Externalizing, Internalizing, Dysregulation, Competence Domains; Atypical and Social relatedness Items Clusters	High percentages of "of concern" scores in Competence Domain Atypical and Social relatedness Items Clusters; trend towards significant difference between maternal and paternal continuous score on the Internalizing Domain.
Ben-Sasson et al. 2008(observational cross-sectional ; same cohort of Ben-Sasson 2007)	ASD: n= 170 m: 78 %, f: 22 % (28±4; 18-33)	To define sensory clusters in toddlers with ASDs Examine eventual correlations between sensory pattern and affective symptoms	ITSP (Dunn, 2002) ITSEA (Carter & Briggs-Gowan, 2006) ADI-R (Lord et al., 1994) ADOS-G (Lord et al., 2002) Mullen Scales of Early Learning (Mullen, 1995)	"Of concern" ITSEA: 61% depression/withdrawal; 30 % negative emotionality; 14% separation distress; 18% inhibition to novelty; 5% anxiety with higher frequency in a subgroup with high frequency of sensory behaviors (under and over responsivity, seeking). Depression/withdrawal only partially referred to ASD symptoms
Visser et al. 2007 (Observational case-control)	ASD: n=36 m: 86%; f: 14% (41,6±8,7) Externalizing	Utility of ITSEA in preschooler referred for	ITSEA (Carter &Briggs-Gowan 2000) CBCL/2-3	Higher Externalizing (Domain and scales) scores particularly in Externalizing group but

	(EXT): n=24 m: 70,8%; f: 29,2% (38,0±10,1) Internalizing (INT): n=16 m: 68,8%; f: 31,2% (41,6±7,2) No diagnosis (No): n=24 m: 77,8%; f: 22,2% (30,2±9,4)	child psychiatric evaluation	(Achenbach, 1992; Koot et al., 1997) CBCL/4-19 (Achenbach, 1991 ; Verhulst et al., 1996) PSI (Abidin, 1983 ; Dutch version : De Brock et al. , 1992) Developmental level: Bayley-II (Bayley, 1993)/Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983)/PEP-3 (Schopler et al. 1990)/VABS (Sparrow et al. 1984)	also in Internalizing group. Significant differences with ASD; Higher Internalizing scores (Domain and Depr-Witdrawal scale) differentiating INT from EXT and No, but not from ASD; Lower Competence (Domain, Imitation-Play, Empathy, Prosocial peer scales) in ASD group Social Relatedness cluster only differentiated ASD from No
Green et al. 2012 (observational longitudinal; same cohort of Carter et al.2007, Ben-Sasson et al. 2007, 2008)	ASD: n= 149 m: 79,2 %, f: 20,8 % (28,3±5,5)	To examine association between anxiety and sensory over responsivity (SOR) in young children with ASD over time (1 year)	ADI-R (Lord et al., 1994) ADOS-G (Lord et al., 2002) Mullen Scales of Early Learning (Mullen, 1995) ITSEA (Carter & Briggs-Gowan, 2006): General Anxiety and Sensory Sensitivity scales Center for Epidemiological Studies-Depression Scale (CES-D, Radloff 1977) Beck Anxiety Inventory (BAI, Beck et al. 1988)	ITSEA Anxiety and Sensory Sensitivity are used as measures of anxiety and SOR. SOR remained stable over time, anxiety significantly increased. More clinically concerning scores in SOR in respect to Anxiety, especially at time 1 SOR predicted increases in anxiety
Ben-Sasson et al. 2013 (observational	ASD: n= 174 m: 78 %, f: 22 % (28,5±3,9; 18-33)	Describe the associations between early	ADOS-G (Lord et al., 2002) Mullen Scales	significant differences in ITSEA anxiety and ITSEA externalizing

longitudinal ; same cohort of Carter et al. 2007, Ben-Sasson et al. 2007, 2008)		Sensory over responsivity (SOR) with parenting stress and family life impairment beyond baseline diagnostic characteristics, child anxiety and externalizing symptoms and maternal affective symptoms	of Early Learning (Mullen, 1995) ITSEA (Carter & Briggs-Gowan, 2006): General Anxiety and Sensory Sensitivity scales ITSP (Dunn, 2002) Center for Epidemiological Studies-Depression Scale (CES-D, Radloff 1977) Beck Anxiety Inventory (BAI, Beck et al. 1988) Family Life Impairment Scale (FLIS, Briggs-Gowan et al. 1998)	between SOR group and non SOR group indicating higher level of anxiety and externalizing symptoms in SOR toddlers

Table 2 BITSEA in ASD population

Study (Design)	Groups (mean age±SD; range)	Main aims	Measures	Results regarding BITSEA
Karabekiroglu et al. 2010 (observational case-control)	Total referred n= 112 m: 70,5 %, f: 29,5 % (29,86±7,31; 14-42); Subsequent diagnosis: No dx n=21 Autism n=35 Disruptive Behavior Disorder n= 15 Anxiety/Depression n= 12 Control (community sample, previous study Karabekiroglu et al. 2009)n= 462 m: 54,5 %, f: 45,5 % (24,60±7,93; 12-42)	Validity and reliability of BITSEA in a clinical sample	BITSEA (Carter &Briggs-Gowan2002; Turkish validated Karabekiroglu et al. 2009) CBCL/2-3 (Achenbach, 1992; Turkish version Erol et al. 2005) Autism Behavior Checklist (AuBC, Krug et al. 1980) Aberrant Behavior Checklist-	Significantly lower BITSEA Competence in Autism group compared to others clinical groups

			Community (ABC, Aman et al. 1987) Infant and Toddler Mental Status Examination (ITMSE, Benham 2000)	
Kruizinga et al. 2014 (observational case-control)	ASD n= 159 m: 79,2 %, f: 20,8 % (31,8 ±6,4) Control(community sample, previous study Kruizinga et al. 2012) n= 3170 m: 51,1 %, f: 48,9 % (23,7±0,7)	To evaluate the screening accuracy of both the BITSEA Problem and Competence scales with regard to an ASD diagnosis	ITSEA (Carter & Briggs-Gowan, 2006): answers on BITSEA items were extracted from ITSEA items	ASD-sample scored lessfavorably on the Problem scale (t =28.1, p,0.001), the Competence scale (t= 29.9, p,0.001) and Autism score (t= 37.3, p, 0.001). (Autism score was calculated by the Authors of this study) The area under the ROC curve (95%CI) of the Problem scale was 0.90(0.87–0.92), of the Competence scale 0.93(0.91–0.95), and of the Autism score 0.95(0.93–0.97). For the total population, the screening accuracy of the Autism score was significantly better, compared to the Problem scale, but not compared to Competence scale. The screening accuracy of the Competence scale was significantly better for girls (AUC = 0.97; 95%CI = 0.95–0.98) than for boys (AUC = 0.91; 95%CI = 0.88–0.94)
Green and Carter 2014 (Observational longitudinal; same cohort of Carter et al. 2007	ASD: n= 162 m: 79,5 %, f: 20,5 % (28,2±4,2; 18-33)	To examine the development of daily living skills across 3	ADI-R (Lord et al., 1994) ADOS-G (Lord et al., 2002) Mullen Scales of Early	BITSEA Problem predicted actual daily living skills, but not the daily skills leaving trajectories, namely children with

?)		years in young children with ASD and its relation with child characteristic and parenting stress	Learning (Mullen, 1995) VABS (Sparrow et. al., 1984) BITSEA (Carter & Briggs-Gowan, 2006) PSI(Abidin, 1983)	more problem behavior didn't show to gain daily leaving skills at a lower rate.

4.2.2 PREVIOUS APPLICATION OF AN ITALIAN VERSION OF THE ITSEA

We have previously reported some results of the clinical application of an Italian version of the ITSEA, both in a clinical group with a diagnosis of Dysregulation Disorder of Sensory Processing (DC: 0-3R) and in a comparison between this clinical group and in a smaller group of children with Autism Spectrum Disorder.

Regulatory disorder and its phenotypic expression: a clinical experience

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Infanzia e Adolescenza. 2012; 11(3): 189-201.

Background The progressive emergence of self-regulation system during the first years of life plays a central role in the development. Self-regulation is a crucial meeting point where genetic constitutionality and environment interface, in early age this interaction mainly takes place in child-caregiver relationship. The presence of anomalies in the self-regulation system have been recognized in the Diagnostic Classification: 0-3 as a specific disorder: Regulation disorders of sensory processing; data about features, boundaries and evolution of DR is still limited.

Objective The main aim of this paper consists in contributing to the definition of phenotypic expression of Regulation Disorders of Sensory Processing, in particular we examined data provided by the clinical assessment tools.

Methods Observational cross sectional study. A group of 27 children who have received a diagnosis of Regulation Disorders of Sensory Processing according to the Diagnostic Classification 0-3R(DC: 0-3R) was selected from children referring to the preschooler psychiatric unit "Cerco Asilo" of IRCCS- Stella Maris Institute; the assessment was supported

by the use of parent questionnaires (CBCL, PSI, ITSEA). A qualitative analysis of the resulting profiles was made both within the general DR group and within the DR subtypes; a correlation analysis between the instruments were also made.

Results Difficulties concerning the externalizing area, the attentional skills and the withdrawal area were detected by questionnaires' profiles; these aspects were differently represented in the three sub-type of DR. The ITSEA seems to be a sensitive tool for the identification of developmental anomalies as it provides a global assessment that includes evaluation of competencies.

Conclusions The findings of the present study confirm the utility of this nosographic entity to describe some developmental atypia in early childhood, also in order to follow up the children's evolutive trajectories.

Clinical use of the Infant-Toddler Social and Emotional Assessment in Autism Spectrum Disorder. IMFAR 2013. 2-4th May 2013 Donostia, San Sebastian Spain

Mottes E., Conti E., Apicella F., Cosenza A., Igliozzi R., Maestro S., Narzisi A., Tancredi R., Muratori F.

Background Studies suggest that a diagnosis of Autism Spectrum Disorder (ASD) can be reliably made in the second year of life being relatively stable over time; at the same time ASD diagnosis of young children can be complex in reason of different presentations and a less specific symptomatology overlapping temperament difficulties, emotional dysregulation, regulatory and attentional problems, cognitive and language delay. As a consequence there is a need for tools to support the characterization and identification of young children with or suspected of an ASD. The main aim of this paper is to determine the capacity of the ITSEA in identifying toddlers with a diagnosis of ASD.

Methods ITSEA is a parental questionnaire performing a profile composed of 3 areas of Problems (Externalizing, Internalizing and Regulatory processes) and an area of Competencies. Each area is composed by different subscales, and three global item clusters (Maladaptive; Social relatedness and Atypical behaviors) can be obtained. Specifically two out of three item cluster refer to typical autism symptomatology).

Subjects were recruited at the ASD division and Cerco Asilo Section of the Stella Maris Scientific Institute following the subsequent inclusion criteria: i) younger than 36 months; ii) diagnosis of ASD according to DSM-IV criteria confirmed with ADOS- G administration; iii)diagnosis of Regulation Disorders of Sensory Processing(REG) based on CD-0:3 R. Patients with any medical or neurological illness were excluded.

Analysis: qualitative comparison between mean scores of ASD group and ASD group from original ITSEA validation study and statistical comparison (T-test for independent groups) between ASD group and REG group.

Results Abnormal scores resulted in at least one subscale or cluster in 100% questionnaires in **ASD** group. The ITSEA profiles in **ASD** group resulted similar to the original ITSEA **ASD** group. As expected clinical scores were obtained on Social Relatedness, Atypical Item Clusters and in the Depression/Withdrawal subscale, even if with lower percentages in respect to ITSEA ASD group. Competence domain was globally involved in 77% of cases.

Higher percentages of abnormal scores resulted in the Aggression/Defiance subscale, in the Negative Emotionality subscale, which is related to a temperamental component and to the difficulty in modulating negative emotional response and in the Eating subscale.

In the comparison with REG group significant differences were found in the Externalizing Domain ($p<.05$), in the Competence Domain ($p<.05$), in the Withdrawal subscale ($p<.01$) and in the Atypical Item clusters ($p<.05$).

ConclusionsThe results of this preliminary clinical application of ITSEA suggests a good capacity of the questionnaire in detecting Toddlers with ASD, providing a profile in which both specific ASD manifestations (Social Relatedness, Atypical Behaviors, Withdrawal) and a global competencies impairment, temperamental and regulatory components may be highlighted.

Significant differences were found in the comparison between ASD group and REG group suggesting a capacity of the tool in differentiate the two clinical groups.

Other studies are required to confirm these results in order to suggest ITSEA as a diagnostic tool supporting clinical assessment for ASD in toddlers.

Part 2

Clinical application

Chapter 5 Application of ITSEA in an Italian clinical population

5.1 Methods

5.2 Results

5.2.1 ITSEA profile in ASD Toddlers (age, gender, development)

5.2.2 Comparison with Typical Development: screening accuracy, sensitivity and specificity

5.2.2.1 ITSEA

5.2.2.2 BITSEA

5.2.3 Comparison with other clinical referred groups: sensitivity and specificity

5.2.3.1 Comparison with Developmental Delay

5.2.3.2 Comparison with Other Psychiatric Disorders

5.2.3.3 Comparison with the overall non-ASD group

Chapter 6 Discussion and conclusions

Chapter 5

Application of ITSEA in an Italian clinical population

In this part of the thesis the results of the application of an Italian version of the ITSEA are reported.

The main aim of the study was to define the profile of ITSEA in a population of children under the age of three (range age 14-35 months) with Autism Spectrum Disorders (already diagnosed with ASD or referred for a suspicious of ASD which was subsequently confirmed).

The objective is developed through the subsequent points:

- Description of ITSEA profile in our ASD sample; the percentage of "of concern" scores (scores above the clinical cut off) are reported. The ITSEA profile of our sample has been qualitatively compared to the Autistic Disorder sample provided in the ITSEA Manual (Carter and Briggs-Gowan, ITSEA Examiner's Manual, 2006);the effect size of differences between the mean scores has also been calculated;
- Analysis of the ITSEA profile in age (under and above 24 months), gender and developmental level subgroups;
- Comparison with a Typical Developmental Control Group, reporting data on accuracy, sensitivity and specificity both in the whole ASD group and in age (under and above 24 months) subgroups;
- Comparison with a clinical referred control group (i.e. Developmental Delay and other Psychiatric Disorders), reporting preliminary data on ITSEA capacity to distinguish between different clinical conditions.

Chapter 5.1

METHODS

Procedure and Participants

ITSEA Italian translation: two independent forward translations were produced by two team, comprised of senior child psychiatrists and clinically trained child psychologist experts in the

areas of social-emotional development, psychopathology and Autism Spectrum Disorder in early childhood. The final version was obtained after comparison of the two forms, in case of disagreement the discrepancies were reexamined and a consensus translation was established.

In a period comprised between January 2010 and January 2015 an Italian translation of the ITSEA (Carter & Briggs-Gowan, 2006) was distributed to the parents of children aged 12 to 35 months, referred to the Clinical Department of Developmental Neuroscience of IRCCS Stella Maris (Autism Spectrum Disorder Section, Early Infant Neurology Section, "Cerco Asilo" Service, a section dedicated to infancy and early childhood intervention with a child-caregivers relation centered approach). The access to our tertiary care center was motivated by a developmental concern, a suspicious of Autism Spectrum Disorder, and other behavioral-emotional problems or because of a previous diagnosis of Autism Spectrum Disorder, Developmental delay or other psychiatric diagnoses.

Three samples of children (Autism Spectrum Disorders (ASD); Developmental Delay (DD); other diagnosis of psychiatric disturbances (OPD)) were recruited from the clinical referred population; a control group of children with typical development (TD) was collected in four urban kindergartens in two different areas, in Tuscany and in Lazio. The description of the four groups is reported in tables 1 and 2.

Parents of the clinical referred children were asked to complete the questionnaire at the beginning of the period of evaluation, together with other questionnaires part of the routine clinical assessment.

Parents in the TD group filled out the ITSEA and CBCL ½-5 (Achenbach &Rescorla, 2000) questionnaires in an anonymous way at kindergarten.

Table 1. Clinical and typical development groups: age and gender characteristics

	ASD (n=88)	**TD (n=60)**	**DD (n=24)**	**OPD (n=27)**
AGE (months)				
Mean (SD)	28.13 (5.96)	26.80 (6.32)	27.83 (6.17)	25.04 (7.01)
Range	14-35	13-35	13-35	13-35
GENDER				
Male (%)	74 (84.1)	43 (71.7)	18 (75.0)	19 (70.3)
Female (%)	14 (15.9)	17 (28.3)	6 (25.0)	8 (29.7)

Table 2. Clinical and typical development groups: gender percentages in under and above 24 months

	ASD (n=88)	TD (n=60)	DD (n=24)	OPD (n=27)
< 24 (%)	23 (26.1)	17 (28.3)	6 (25.0)	11 (40.7)
Male (%)	19 (21.6)	15 (25.0)	2 (8.3)	10 (37.0)
Female(%)	4 (4.6)	2 (3.3)	4 (16.7)	1 (3.7)
>24 (%)	65 (73.9)	43 (71.7)	18 (75.0)	16 (59.3)
Male (%)	55 (62.5)	28 (46.7)	16 (66.7)	9(33.3)
Female (%)	10 (11.4)	15 (25.0)	2 (8.3)	7 (25.9)

In the ASD group were included 88 children (mean age 28.1 mo, SD 5.6 mo) who have been evaluated by a multidisciplinary team including a senior child psychiatrist, an experienced clinically trained child psychologist and a speech-language pathologist; when the child was assessable in standardized conditions, the clinical assessment was completed with a standardized evaluation to confirm the ASD clinical diagnosis (ADOS-G (Lord et al., 2000) or ADOS-2 (Lord, Rutter et al., 2012), n=67) and with a standardized psychometric (developmental/cognitive) assessment (n= 56).

As part of the diagnostic flow-chart children with a diagnosis or suspected of ASD also performed protocol of tests including auditory evaluation, EEG, genetic analysis (DNA analysis of FRA-X, high resolution karyotype/array CGH), and screening tests for inborn errors of metabolism. Inclusion criteria in the ASD sample were: i) confirmed/first diagnosis of ASD according to DSM-IV/DSM-5 criteria (American Psychiatric Association, 2000; American Psychiatric Association, 2013), ii) 12-35 months of age, iii) no neurometabolic, neurological, genetic, significant sensory impairment conditions.

The second group (DD) consisted of 24 children (mean age 27.8 mo, SD 6.2 mo) who received a diagnosis of Developmental Delay after a multidisciplinary team assessment including a senior child neuropsychiatrist, and experienced clinically trained child psychologist.

Inclusion criteria were: i) confirmed/first diagnosis of developmental delay based on a standardized developmental assessment (Bayley Scales or Griffiths Scales), ii) 12-35 months of age. ASD was actively ruled out on the basis of the clinical evaluation, supported, when the children were assessable, by the ADOS-G/ADOS 2 assessment.

The third group (OPD) is comprised of 27 children (mean age 25.0 mo, SD 7.0 mo) who received a psychiatric diagnosis after a multidisciplinary team assessment including a senior child psychiatrist, and experienced clinically trained child psychologist. Parents in this group

of patients completed ITSEA and CBCL questionnaire, together with other questionnaires part of the routine clinical assessment.

Inclusion criteria were: i) a psychiatric diagnosis according to the CD: 0-3 classification systems (Zero TO Three, 2005), ii) 12-35 months of age. ASD was actively ruled out on the basis of the clinical evaluation; children with a Disorder of Relating and Communicating, according to DC: 0-3, or who showed some characteristic of ASD were excluded, even if assessment data supporting an ASD diagnosis were inconsistent; moreover children who obtained clinical or borderline values in the "Withdrawn syndrome scale" and in the "Pervasive Developmental Problems DSM-oriented scale" were not included according to the reported study concerning the use of CBCL in ASD toddlers (Narzisi et al. 2013) that suggests that high scores in these scales can be indicative of ASD. In table 3 the diagnostic characterization of the sample is reported.

The control group of typical development is comprised of 60 children (mean age 26.8, SD 6.3). Data were collected in four urban kindergartens in two different areas (Tuscany and Lazio): parents of 88 children completed the ITSEA and CBCL questionnaires; children with whatever borderline or clinical score at the CBCL were excluded (n=6).Chi square test was performed in order to define the number of females and males needed to obtain an group homogeneous with the ASD group relative to gender. From the left 81 children 43 male and 17 female were randomly extracted.

Table 3. Other Psychiatric Disorders: diagnoses

	n
OPD (DC: 0-3R)	27
Posttraumatic Stress Disorder	1
Disorders of Affect	6
Regulation Disorder of Sensory Processing	13
Sleep/Feeding Behavior Disorders	7

Measures

ITSEA (Carter and Briggs-Gowan, 2006) is a parent-rated measure of social-emotional problems and competencies in children 12 to 35 months old. It is comprised of 169 items rated on a 3-point scale: not true/rarely, somewhat true/sometimes, very true/often. It includes three Problems Domains (Externalizing, Internalizing and Dysregulation) and one Competence Domain, each of which are composed by scales (Externalizing: Activity/Impulsivity, Aggression/Defiance, Peer Aggression scales; Internalizing:

Depression/Withdrawal, General Anxiety, Separation Distress, Inhibition to Novelty scales; Dysregulation: Negative Emotionality, Sleep, Eating, Sensory Sensitivity scales; Competence: Compliance, Attention, Mastery Motivation, Imitation/Play, Empathy, Prosocial Peer Relation scales). The profile is also composed of three Item Cluster (Maladaptive, Social Relatedness and Atypical Item Cluster) that include infrequent behaviors referring to specific psychopathological conditions; particularly the Social Relatedness and the Atypical Item Clusters refer to the Autism spectrum symptomatology. Completion requires approximately 30 minutes. To minimize response set biases, problem and competence items are interwoven throughout the ITSEA

ITSEA has been nationally standardized (Carter & Briggs-Gowan, 2206); for each of the ITSEA domain T-scores are available and scaled scores for the subscales within 6 month age by sex groupings. A T score ≥ 65 for the broad domains and a 90^{th} percentile cut point for the subscales have been established to indicate the "of concern" scores. For what concern psychometric property, the ITSEA subscales and domain have established acceptable internal consistency (Cronbach's alphas from .52 to .90); test-retest reliability and inter-rater agreement have been evaluated using the Intraclass Correlation Coefficient (ICCs in the overall group from .64 to 90 and from .44 to .83, respectively). Validity has been established on the basis of the study of correlation within domains and scales and relative to observational measures and other parent-report checklists.

BITSEA (Briggs-Gowan& Carter, 2006) is comprises of 42 items that are drawn from the longer ITSEA and that are divided into a 31-item Problem Scale and an 11-item Competence Scale; the response format is a 3-point scale; 5 to 7 minutes are requested for the completion. As like ITSEA, BITSEA has been standardized and normed based on a nationally representative sample. BITSEA screening cutpoints are designed to broadly capture children with potential problems that merit additional follow-up and/or assessment. The Problem cutpoint is designed to identify children with scores at or above the 75th percentile in the normative birth cohort; the Competence cutpoint is designed to identify children with scores in the lowest 10th–15th percentile relative to the birth cohort. Different cutpoints are available for gender and age-bands. BITSEA has demonstrated moderately acceptable internal consistency Cronbach's =.79 for Problems and .65 for Competence (Briggs-Gowan et al., 2004); according to the Manual the test-retest reliability is good-to-excellent (r .92 for the Problem Total score and .82 for the Competence Total score) and the inter-rater agreement is good (ICC from.70 to .78 for girls for the Problem Total score; .58 for girls and .67 for boys

for the Competence Total score). Similar to the findings for the ITSEA, BITSEA Problem scale and Competence scales have demonstrated validity relative to parental reports of problems on other standardized measures, as well as in relation to special group studies (Briggs-Gowan et al., 2004; Briggs-Gowan& Carter, 2006).

The CBCL 1½–5 (Achenbach &Rescorla, 2000; Frigerio et al., 2009) is a parent-report measure designed to record the behavioral peculiarities of preschoolers. It is comprised of 100 items rated on a 3-point response scale (0, not true; 1, somewhat or sometimes true; 2, very true or often true). The measure provides scores for three summary scales (i.e., Internalizing, Externalizing and Total Problems), seven syndrome scales (i.e., Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior), and five DSM-Oriented scales (i.e., Affective Problems, Anxiety Problems, Pervasive Developmental Problems, Attention Deficit/Hyperactive Problems and Oppositional Defiant Problems). A T-score of 63 and above for summary scales, and 70 and above for syndrome and DSM-Oriented scales, are generally considered clinically significant. Values between 60 and 63 for summary scales, or between 65 and 70 for syndrome and DSM-Oriented scales, identify a borderline clinical range. Values under 60 for the summary scales or under 65 for other scales are not considered clinically significant. For what concern psychometric property, the CBCL has demonstrated very good 8-day test–retest reliability (mean r = 0.84); interparent agreement (mean r =0.61) and discriminative validity in distinguish between referred and non-referred children.

The ADOS (ADOS-G Lord et al., 2000; ADOS-2; Lord et al. 2012) is a semi-structured play based assessment considered the ‘gold standard’ diagnostic tool for ASD. Different modules are designed to be administered to different individuals based on their age and language development. In our study Module 1 of ADOS-G and of ADOS-2 and Toddler Module of ADOS-2 were used.

The developmental/cognitive assessment was performed with one of the subsequent measures: Griffiths Mental Developmental Scales (Griffiths, 1984), Bayley Scales of Infant Development 3rd Edition (Bayley, 2005), Leiter-R (Roid & Miller, 1996), Wechsler Preschool and Primary Scale of Intelligence, Third Edition (Wechsler D., 2003).

Analysis

The subsequent analyses have been performed:

Characterization of ASD sample

- Descriptive comparison with the Autistic Disorder group (AD) provided in the ITSEA Examiner's Manual. A summary profile for an Autistic Disorder sample (AD, n=33) is provided in the ITSEA Examiner's Manual (Carter and Briggs-Gowan, 2006). The mean raw scores represent the average scores for the entire group across ages; the scores are considered "of concern" if they are in the cut score range that correspond to the cut scores for the respective subscales across all ages and for both sexes; the percentages reported represent the percentage of children in the group whose scores were in the "of concern" area (see Table 4).

  In the present study we applied the same methodology to our ASD sample and we compared the results with those reported in the ITSEA Manual for the AD sample.
- Effect sizes of the differences between mean scores of the ASD sample and the AD Manual sample
- Descriptive analysis of the percentages of "of concern" scores (above the cut off) in the whole ASD sample and in the age subgroups (under and above 24 months).
- Comparison (T-test for independent groups) of mean scores in female and male subgroups of the whole ASD sample.
- Comparison (ANOVA, Bonferroni post-hoc) of the mean scores in three subgroups based on nonverbal developmental level: group 1: non verbal developmental quotient under -1DS; group 2: non verbal developmental quotient above -1DS: group 3: developmental level non evaluable with standardized assessment.

Comparison with a Typical Developmental Control Sample

ITSEA:

- Statistic comparisons (T-test for independent groups) between the overall ASD and TD groups and between ASD and TD age subgroups (under and above 24 months).
- Screening accuracy for the indices that showed statistically significant differences ($p<.001$) and the larger effect sizes was evaluated by calculating the Receiver Operating Characteristic (ROC) curves, with ASD group as the reference group.

  The ROC curve is a plot of sensitivity as a function of 1-specificity for all possible cutpoints. The greater the area under the curve (AUC), the more discriminative the scores are. According to Cicchetti et al. (1995) recommendations, diagnostic accuracy

implied by an AUC score is Poor when less than .70, Fair when between .70 and .79, Good when between .80 and .89 and Excellent when above .90.

Sensitivity, specificity, positive and negative predictive values have been calculated for different cutpoints. The criteria of Cicchetti et al. (1995) can be applied for the evaluation of sensitivity and specificity.

BITSEA: In a recent study (Kruizinga et al. 2014), the screening accuracy for ASD of the BITSEA has been evaluated. As proposed in the cited paper, we extracted the items of which BITSEA is comprised from the larger pool of ITSEA items.

- Differences in Problem and Competence BITSEA mean scores between ASD and TD have been tested with T-test for independent samples.
- Screening accuracy has been evaluated by calculating ROC curves, with ASD group as the reference group.

  Sensitivity, specificity, positive and negative predictive values, have been calculated for different cutpoints.

Comparison with clinical referred control groups (i.e. Developmental Delay and other Mental Health Problems)

- Comparison (T-test for independent groups) between ASD and non-ASD (DD plus OPD).
- The Receiver Operating Characteristic (ROC) curves were calculated for indices that showed statistically significant differences ($p<.001$) and the larger effect sizes.
- Comparison (ANOVA, Bonferroni post-hoc) between ASD, DD and TD and between ASD, OD and TD were also performed.

All statistic analyses were carried out using SPSS version 22.0 for windows (SPSS Inc., Chicago, IL, USA).

Chapter 5.2

5.2.1 ITSEA PROFILE IN ASD TODDLERS

Autism Spectrum Disorder group and ITSEA Manual's Autistic Disorder group: a qualitative comparison

The summary profile for the Autistic Disorder group of the ITSEA Manual is characterized by a global deficit in the Competence Domain and subscales; "of concern" scores are evident also in the Maladaptive, Social Relatedness and Atypical Item Clusters; within the Problems Domains, in the Depression/Withdrawal subscale of Internalizing Domain and in the Eating subscale of Dysregulation Domain.

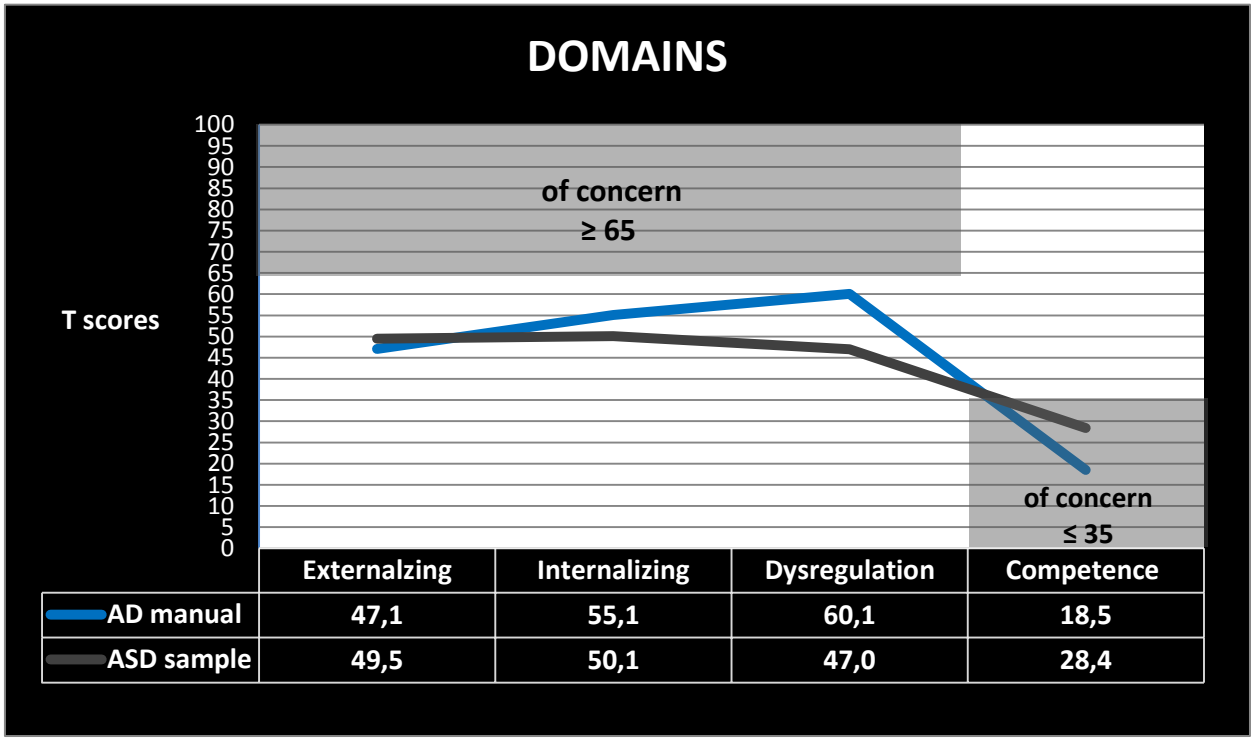
In our ASD group the mean scores resulted in the "of concern" range in the Competence area and in the majority of Competence subscales, in the Depression/Withdrawal scale and in the Social Relatedness and Atypical Item Clusters.As shown in Table 4 the "of concern percentages" in the two groups are different, but the global profile is similar. Within the Internalizing Domain a lower percentage can be observed also in the Inhibition to Novelty scale; within the Dysregulation Domain a similar prevalence of "of concern" scores has resulted in the Negative Emotionality scale, while the percentages in our sample are lower in the other scale (Eating, Sleeping, Sensory Sensitivity).

Table 4: Present study ASD sample and ITSEA Manual's AD sample

	ASD Mean (sd)	Cut score	Of concern	% Of concern	Manual's AD sample Mean (sd)	Cut score	Of concern	% Of Concern
EXTERNALIZING	49.5(12.2)	>65		9.4	47.08(8.4)	>65		
Activity/Impulsivity	.70 (.45)	1.19-1.51		8.0	0.79 (.40)	1.19-1.51		6.06
Aggression/Defiance	.46 (.27)	0.74-0.95		10.6	0.36 (.23)	0.74-0.95		6.06
Peer Aggression	.15 (.20)	0.60-1.07		1.6	0.07 (.12)	0.60-1.07		0
INTERNALIZING	50.1(10.1)	>65		12.6	55.10(11.1)	>65		
Depression/Withdrawal	.35(.28)	0.22-0.39	+	44.3	0.45(.21)	0.22-0.39	+	69.70
General Anxiety	.24(.20)	0.37-0.72		8.2	0.22(.16)	0.37-0.72		3.03
Separation Distress	.92(.42)	1.27-1.56		10.3	0.84(.50)	1.27-1.56		21.21
Inhibition to Novelty	.72(.47)	1.34-1.65		3.8	0.90(.52)	1.34-1.65		12.12
DYSREGULATION	47.0(13.6)	>65		11.4	60.12(15.9)	>65		
Negative Emotionality	.65(.37)	0.91-1.32		19.3	0.73(.38)	0.91-1.32		21.21
Sleep	.45(.46)	1.08-1.38		10.7	0.64(.62)	1.08-1.38		24.24
Eating	.48(.37)	0.75-0.96		18.2	0.85(.44)	0.75-0.96	+	39.39
Sensory Sensitivity	.39(.35)	0.80-1.02		11.6	0.57(.40)	0.80-1.02		18.18
COMPETENCE	28.4(12.2)	<35	+	72.0	18.52(7.0)	<35	+	
Compliance	1.02(.36)	0.68-0.93		37.9	0.83(.42)	0.68-0.93	+	60.61
Attention	.96(.48)	0.43-1.17	+	48.9	0.89(.40)	0.43-1.17	+	54.55
Mastery Motivation	1.30(.43)	0.81-1.30	+	39.5	0.90(.45)	0.81-1.30	+	75.76
Imitation/Play	.80(.48)	0.66-1.35	+	67.1	0.50(.29)	0.66-1.35	+	96.97
Empathy	.50(.41)	0.17-0.90	+	71.3	0.15(.25)	0.17-0.90	+	93.94
Prosocial Peer Relations	.66(.52)	0.17-0.88	+	56.7	0.14(.18)	0.17-0.88	+	96.97
ITEM CLUSTERS								
Maladaptive Item Cluster	.15(.19)	0.17-0.29		28.0	0.19(.16)	0.17-0.29	+	42.42
Social Relatedness Item Cluster	1.32 (.30)	1.27-1.44	+	55.7	1.11 (.22)	1.27-1.44	+	87.88
Atypical Item Cluster	.69(.41)	0.50-0.71	+	55.7	1.02(.27)	0.50-0.71	+	93.94

In Figure 1 the Domains profiles of the ASD sample and of the AD sample of the Manual are graphically represented. In both the profiles the Problems domains don't bottom the of concern cut point, while the Competence Domain is collocated in the "of concern" area. Larger differences in the Dysregulation T score and in the Competence T score are visible.

Fig.1 ITSEA Domains profile ASD sample and AD Manual sample



The effect size of the differences between the means and standard deviations of the two groups have been calculated d Cohen's d): the larger effect sizes have been found for the Dysregulation Domain (.899), particularly in the Eating scale (.910), for the Competence Domain (.993) and its scale Imitation/Play (.757), Empathy (1.03) and Prosocial Peer Relation (1.34) and for the Atypical Item Cluster (.950) and the Social Relatedness Item cluster (.798).
The frequency distribution up to the 25th percentile of the Dysregulation Domain scales and of Imitation/play, Empathy and Prosocial Peer Relation, in comparison with the percentage of scores above the 10th percentile in the AD sample of the manual, are reported in Figure 2 and 3. We can observe that the cumulative percentages at the 15th percentile in the scale Inhibition to novelty, Negative emotionality and sensory Sensitivity overcome the percentages at the 10th percentile in the Manual AD sample; in the Depression/Withdrawal scale the percentage at the 25th percentile overcomes that of 10th percentile in the Manual AD sample; while the

percentages at the 25th percentile in the Sleep, Eating, Imitation/play, Empathy and Prosocial Peer Relation scales, near the 10th percentile of the Manual AD sample.

Fig.2 Frequency distribution

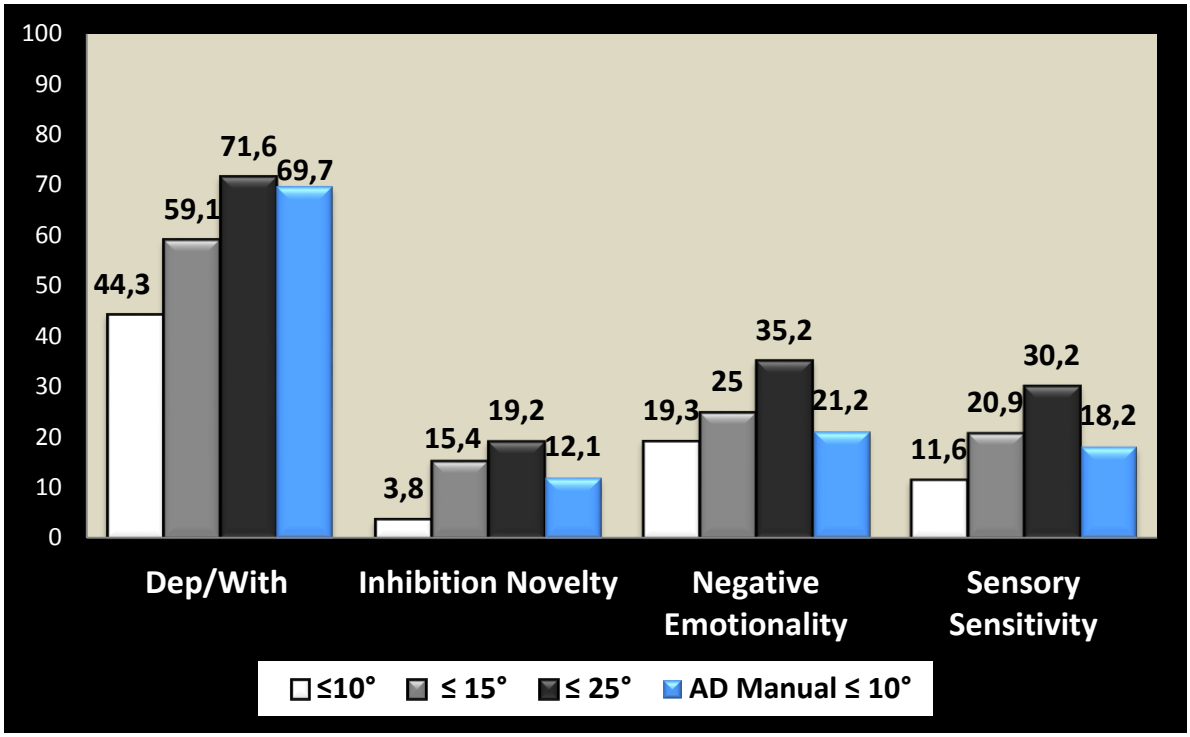
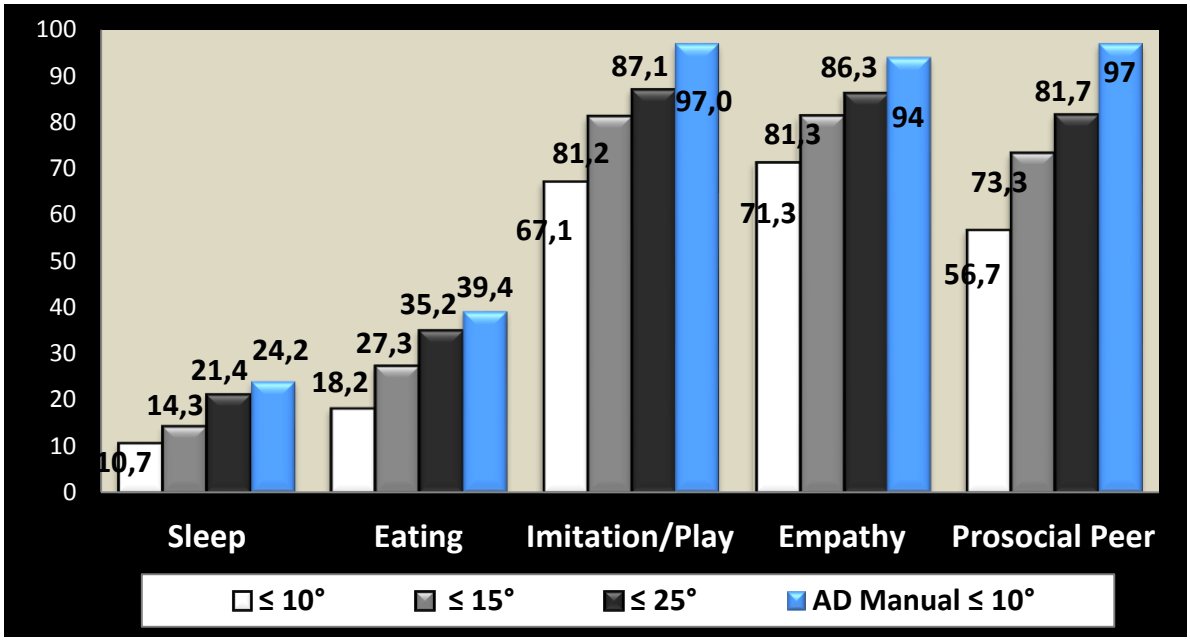


Fig. 3 Frequency distribution



In order to better describe and characterize the ITSEA profile in the ASD group we have carried out analysis comparing subgroups defined by age, sex and developmental evaluation.

Comparison between the Autism Spectrum Disorder subgroups: under and above 24 months of age

As reported in Table 1 and 2, our ASD sample is composed of a subgroup of children under the age of 24 months (meang age= 19.7 months, sd 2.7 months; n=23, 19 (21.6%) male and 4 (4.6%) female) and a subgroup older than 24 months (mean age= 31.1 months, sd 3.4 months; n= 65, 55 (62.5%) male and 10 (11.4%) female).

In table 5 the mean scores of the ASD subgroups defined by the age cut point of 24 months are reported together with the cut score range relatively to age bands 12-23 months and 24-30 months, and the "of concern"percentages in the two subgroups.

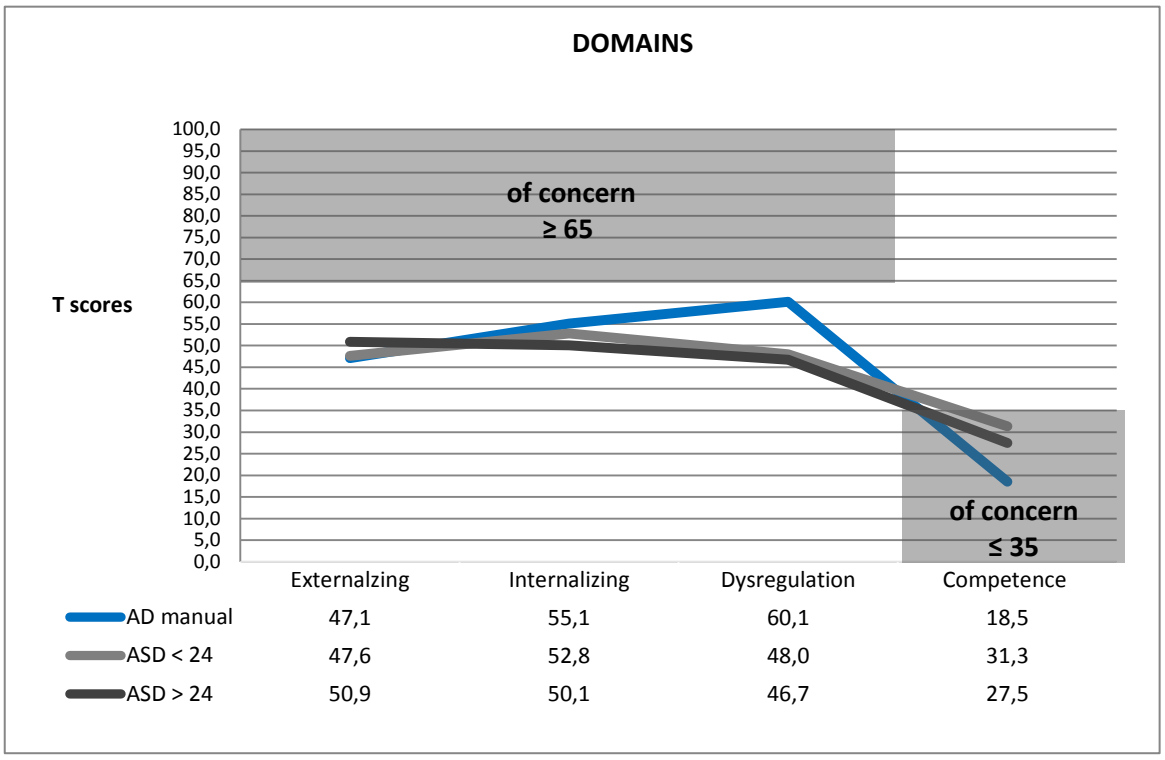
Table 5. ASD < 24 monthsand ASD >24 months

ASD < 24 (n=23) ASD >24 (n=65)	ASD <24 Mean (sd)	Cut score	Of concern	% Of concern	ASD >24 Mean (sd)	Cut score	Of concern	% Of concern
EXTERNALIZING	47.6 (10.0)	>65		4.8	50.9 (12.6)	>65		10.9
Activity/Impulsivity	.67 (.48)	1.19-1.51		8.7	.71 (.44)	1.26-1.42		7.8
Aggression/Defiance	.35 (.24)	0.74-0.87		**5.0**	.49 (.28)	0.79-0.95		**12.3**
Peer Aggression	.15 (.23)	0.60-0.84		0	.15 (.20	0.77-1.07		2.0
INTERNALIZING	52.8 (10.7)	>65		18.2	50.1 (10.0)	>65		10.8
Depression/Withdrawal	.45 (.34)	0.29-0.36	+	60.9	.31 (.24)	0.22-0.39	+	38.5
General Anxiety	.18 (.12)	0.37-0.55		0	.26 (.22)	0.58-0.72		10.9
Separation Distress	.96 (.50)	1.48-1.56		8.7	.91 (.40)	1.27-1.56		10.9
Inhibition to Novelty	.80 (.45)	1.34-1.38		5.3	.69 (.47)	1.45-1.57		3.4
DYSREGULATION	48.0 (12.5)	>65		8.7	46.7 (14.0)	>65		12.3
Negative Emotionality	.66 (.33)	0.96-1.01		26.1	.65 (.38)	0.98-1.32		16.9
Sleep	.48 (.48)	1.17-1.33		13.6	.44 (.46)	1.08-1.38		9.7
Eating	.40 (.32)	0.75-0.91		13.0	.51 (.41)	0.84-0.97		20.0
Sensory Sensitivity	.37 (.32)	0.80-0.91		9.5	.40 (.36)	0.82-1.02		12.3
COMPETENCE	31.3 (10.4)	<35	+	63.2	27.5 (12.7)	<35	+	74.6
Compliance	.88 (.33)	0.68-0.91	+	50.0	1.07 (.36)	0.90-0.93		33.8
Attention	.99 (.48)	0.43-0.91		43.5	.95 (.49)	0.87-1.17	+	50.8
Mastery Motivation	1.42 (.44)	0.81-1.09		28.6	1.26 (.42)	1.18-1.30	+	43.1
Imitation/Play	.57 (.45)	0.66-1.07	+	**89.5**	.87 (.46)	0.88-1.35	+	**61.5**
Empathy	.30 (.29)	0.17-0.51	+	70.6	.56 (.43)	0.60-0.90	+	71.4
Prosocial Peer Relations	.45 (.37)	0.17-0.43		**41.7**	.72 (.55)	0.48-0.88	+	**60.4**
ITEM CLUSTERS								
Maladaptive Item Cluster	.12 (.15)	0.20-0.29		26.3	.16 (.20)	0.17-0.22		28.6
Social Relatedness Item Cluster	1.25 (.30)	1.31-1.38	+	73.9	1.33 (.29)	1.27-1.44	+	49.2
Atypical Item Cluster	.80 (.37)	0.50-0.61	+	**78.3**	.66 (.42)	0.53-0.71	+	**47.7**

At a qualitative comparison the profiles of the two groups appear similar. In fact the Competence Domain, the Depression/Withdrawal scale and the Social Relatedness and Atypical Item Clusters remain in the "of concern" range, even if in the younger subgroup

In Figure 4the Domains profiles of the ASD age subgroups and of the AD sample of the Manual are graphically represented. A T-test for independent samples didn't find any significant differences between the domains t scores (p values comprised between .245 and .693).

Fig.4 ITSEA Domains profile in ASD < 24 months, ASD > 24 months and Manual's AD samples



When considering the percentages of "of concern" scores (Table 5) we can observe that in the ASD under 24 months subgroup the percentages are higher in the Depression/Withdrawal scale (60.9 vs 38.5), in the Social Relatedness (73.9 vs 49.2) and Atypical Item Clusters (78.3 vs 47.7) and, within the Competence Domain, in the Compliance (50.0 vs 33.8 %) and Imitation/Play scales (90.0 vs 60). On the contrary the "of concern" percentage in the Competence Domain, in the Prosocial Peer Relation scale and in the Mastery Motivation scale resulted higher in the ASD subgroup above 24 months of age (74.6 vs 63.3, 60.4 vs 41.7, 43.1 vs 28.6 respectively). In the group above 24 months of age, a higher "of concern" percentage, even if with a mean scores under the "of concern" range, has been observed in the Externalizing Domain, particularly in the Aggressive/Defiance scale.

As long as in the normative population a difference in the Depression/Withdrawal scale wasn't found in the comparison for both age bands and gender, we performed a T-test for independent samples to compare the mean scores of the two ASD age subgroups in this scale. The result showed a significant difference ($p<.05$) with an effect size of 0.109. Differences in the comparison between

age bands weren't found in the Atypical and in the Social Relatedness Item clusters either; the T-test between age subgroups didn't find significant differences in this indices.

In order to analyze the differences observed in the "of concern" percentages between the ASD age subgroups, we then considered the distribution of the scores in the Depression/Withdrawal and in the Competence Domain. The same wasn't made for Social Relatedness and Atypical Item cluster because percentile rankings are not provided for these indices, due to the lower internal consistency of the clusters.

Figure 5 shows the frequency distribution of the Depression/Withdrawal scale's scores considering the subsequent classes: scores equal or under the 10^{th} percentile of the normative sample, scores between the 10^{th} and 25^{th} percentile; scores above the 25^{th} percentile.

The cumulative percentages of the scores under the 25^{th} percentile of the normative distribution are of 78.3 %, 69,3% and 71,6% in the ASD under 24 months sample, in the ASD above 24 moths and in the overall ASD sample, respectively.

Fig.5 Depression/Withdrawal scale: frequency distribution.

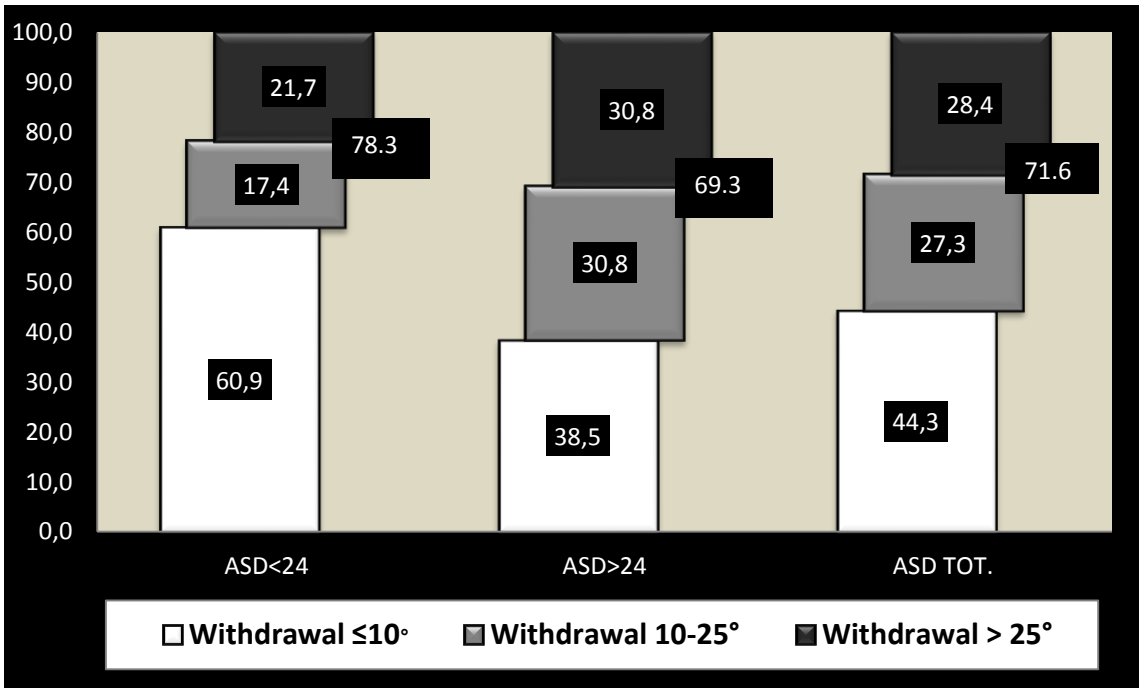
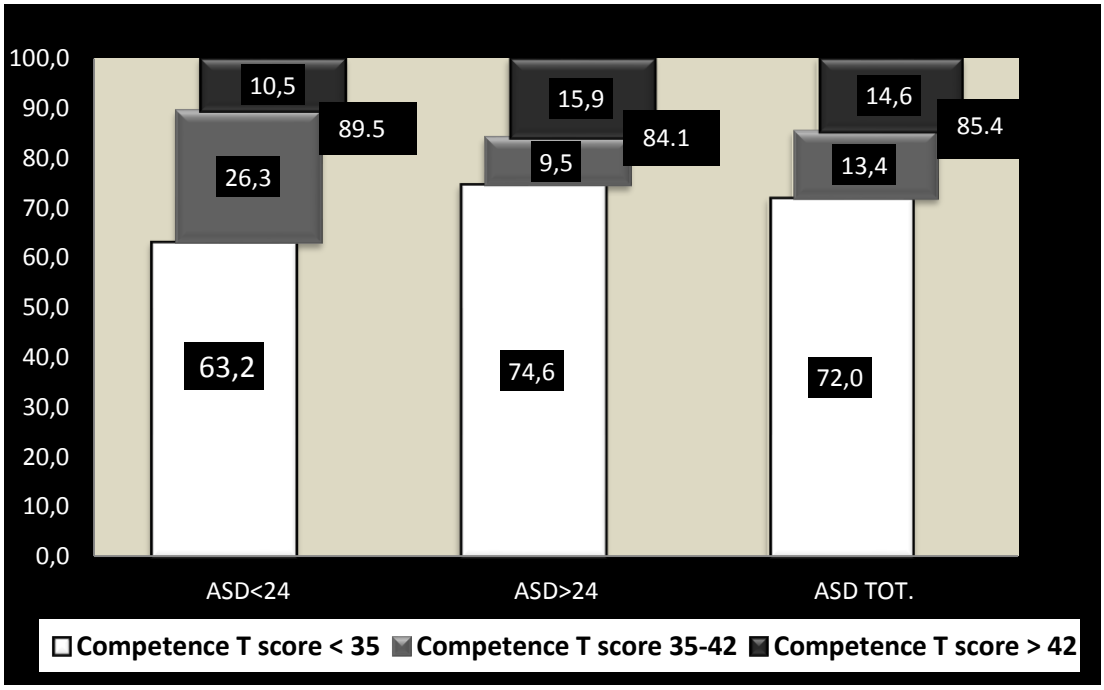


Figure 6shows the frequency distribution of the Competence Domain T scores considering the subsequent classes: scores equal or under a T score of 35; T scores between 35 and 42; T scores above 42. (The cumulative percentage correspondence of a T-score of 42 in the normative age and gender bands distribution is as it follows: 26. 1 for female 12-17 months, 28.2 for female 18-23

months, 24.7 for female 24-29 months, 25.7 for female 30-35 months, 24.6 for male 12-17 months, 20.9 for male 18-23 months, 21.1 for male 24-29 months, 25.7 for male 30-35 months.)

The cumulative percentage of the T-scores under 42 is of 89.5 %, 84.1 % and 85.4 % respectively in the ASD under 24 months sample, in the ASD above 24 moths sample and in the overall ASD sample.

Fig.6 Competence Domain: frequency distribution



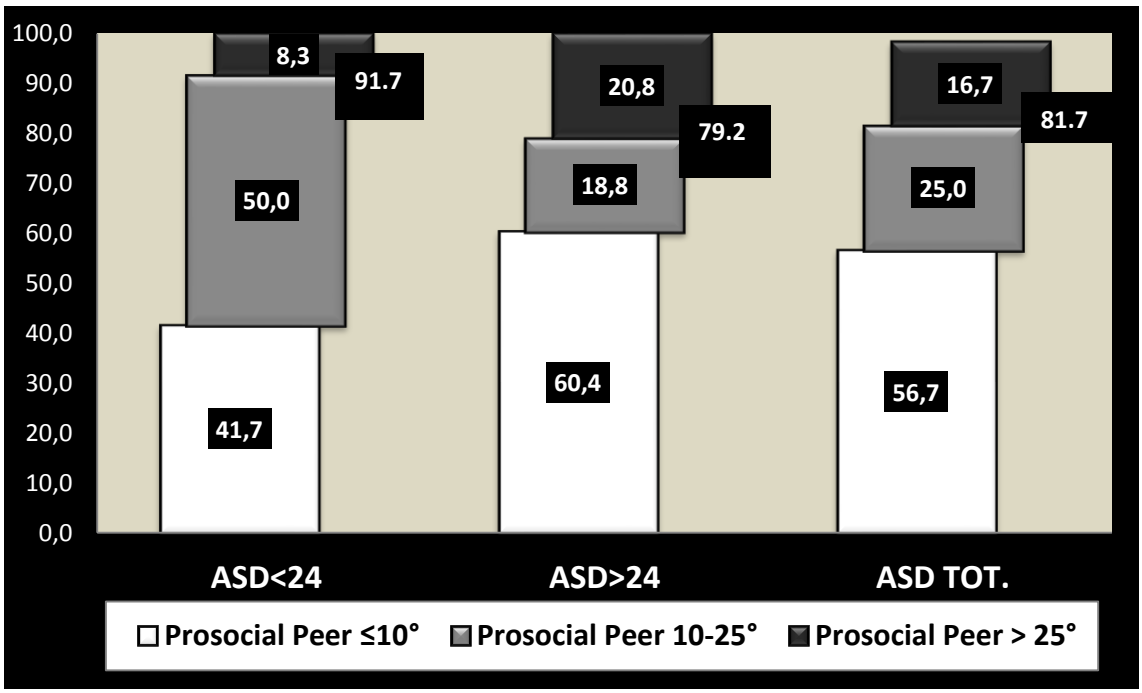
Within the Competence Domain we examined the frequency distribution of the two scales that showed the greater difference relatively to the "of concern" percentages, namely the Imitation/play scale (percentages "of concern": 89.5 in the under 24 months group and 61.5 in the above 24 months group) and the Prosocial Peer Relation scale (percentages "of concern": 41.7 in the under 24 months group and 60.4 in the above 24 months group). In Figure 7 and 8 the frequency distribution of these two scales are represented considering the classes: scores equal or under the 10th percentile of the normative sample, scores between the 10th and 25th percentile; scores above the 25th percentile.

The cumulative percentages of the scores under the 25th percentile of the normative distribution for the Imitation/Play scale are of 89.5 % in the ASD under 24 months sample, of 87.7 % in the ASD above 24 moths and of 88.1 % in the overall ASD sample.

Figure 7. Imitation/Play scale: frequency distribution

The cumulative percentages of the scores under the 25th percentile of the normative distribution for the Prosocial Peer Relation scale are of 91.7 % in the ASD under 24 months sample, of 79.2 % in the ASD above 24 moths and of 81.7 % in the overall ASD sample.

Figure 8. Prosocial Peer Relation scale: frequency distribution



Comparison between the Autism spectrum Disorder subgroups: gender

As reported in Table 1 and 2 the percentages of female and male in our ASD sample are respectively of 15.9 (n=14; mean age 28.2, sd 5.4)and of 84.1 (n=74; mean age 28.1, sd 6.1 months). Female and male under the age of 24 months are respectively 4.6 % (n=4) and 21.6 % (19) of the overall sample; female and male above the age of 24 months are respectively 11.4 % (n=10) and 62.5 % (n=55) of the overall sample.

A statistical comparison (T test for independent samples) was performed to examine sex differences. There were no sex differences in any of the ITSEA problem domains, Internalizing, Externalizing, Dysregulation, (all ps> .10); the analysis showed a significant difference for the Competence Domain (female mean T score 21.8, sd 12.7; male mean T score 29.8, sd 11.8; $p<.05, \eta_2$ effect size .124), while the difference was not confirmed for the Competence raw score. There were trends for girls to have higher mean score in the Inhibition to Novelty scale (p=.10)

When comparing (T-test) two groups of 14 female and male matched for age and developmental level, the same results were found for Competence T score and raw score; a higher (p=.005) mean score in Aggressive/Defiance scale was found for male.

Considering the percentages of "of concern" scores, in the Competence Domain 78.6 % of female scores and 70.6 % of male scores resulted below the cut off; in the Depression/Withdrawal scale 71.4 % of female scores and 36.0 % of male scores resulted in the "of concern" area; in the Aggression/Defiance scale 0 % of female scores and 12.7 % of male scores resulted in the "of concern" area.

Comparison between the Autism spectrum Disorder subgroups: developmental assessment

The ASD sample was divided into three subgroups based on the developmental/cognitive assessment: a group of 37 children with a non verbal developmental quotient (nv DQ) below - 1 SD (Group 1: mean age 29.5 months, standard deviation 5.0 months); a group of 19 children with a non verbal developmental quotient (nv DQ) above – 1 SD (Group 2: mean age 26.4 months, standard deviation 6.4 months); a group of 26 children who weren't assessable with a psychometric tool (Group 3: mean age 29.8 months, standard deviation 5.2 months). Six children of the overall sample weren't tested for developmental level with a psychometric assessment.

A comparison (ANOVA, Bonferroni post-hoc) has been performed to examine if these three groups differentiated in any of the ITSEA Domains or scales. There were no differences in any of the ITSEA Problem Domains; in contrast statistically significant differences were found in the overall Competence Domain (T score and raw score; p=.0000) with the strongest difference between the group with nv DQ above – 1 SD and the non assessable group (p=.000); at the scales level within

the Competence Domain the strongest differences can be observed in the Mastery Motivation scale and Empathy scale (p= .000 and p=.005 respectively); the Imitation/Play and Prosocial Peer Relation mean scores resulted significantly different too, with a p value <.05. For all these scales the post-hoc analysis demonstrated the strongest significant difference between Group e and Group 3. The results of this analysis are detailed in table 6.

Table 6. Group 1 (nv D.Q. <-1DS); Group 2 (nv D.Q.>-1 DS); Group 3 (non assessable)

	Gr 1	Gr 2	Gr 3	ANOVA F	ANOVA Sig.	Effect size	Post-hoc 1 vs 2	Post-hoc 1 vs 3	Post-hoc 2 vs 3
	M(SD) n=37	M(SD) n=19	M(SD) n=26						
AGE	29.5 (5.0)	26.4 (6.4)	29.8 (5.2)	3.300	.042	.074	.185	1.000	.069
EXTERNALIZING T	49.3(10.4)	48.3(10.1)	48.1(14.9)	.041	.960	.011	1.000	1.000	1.000
EXTERNALIZING raw	.49(.27)	.46 (.27)	.46 (.37)	.069	.934	.007	1.000	1.000	1.000
Activity/Impulsivity	.75 (.43)	.64 (.42)	.68 (.49)	.321	.726	.030	1.000	1.000	1.000
Aggression/Defiance	.42 (.19)	.46 (24)	.44 (.32)	.157	.855	.032	1.000	1.000	1.000
Peer Aggression	.12 (.13)	.17 (.22)	.14 (.20)	.595	.555	.002	1.000	1.000	.941
INTERNALIZING T	52.2 (8.7)	48.3(10.6)	50.8 (9.7)	1.094	.340	.076	.501	1.000	.983
INTERNALIZING raw	.57 (.20)	.50 (.23)	.55 (.21)	.836	.437	.077	.750	1.000	1.000
Depression/Withdrawal	.42 (.27)	.30 (.29)	.31 (.24)	1.450	.241	.011	.330	.480	1.000
General Anxiety	.29 (.25)	.20 (.18)	.23 (.18)	1.188	.310	.090	.385	.902	1.000
Separation Distress	.87 (.40)	.90 (.48)	.91 (.35)	.068	.934	.069	1.000	1.000	1.000
Inhibition to Novelty	.70 (.39)	.64 (.51)	.80 (.47)	.832	.439	.069	1.000	1.000	.606
DYSREGULATION T	46.3(15.1)	45.0(12.0)	47.7(14.3)	.310	.734	.062	1.000	1.000	1.000
DYSREGULATION raw	.49 (.26)	.49 (.27)	.52 (.26)	.108	.898	.037	1.000	1.000	1.000
Negative Emotionality	.56 (.34)	.62 (.30)	.76 (.47)	1.855	.163	.086	1.000	.224	.427
Sleep	.43 (.43)	.37 (.45)	.46 (.48)	.305	.738	.042	1.000	1.000	1.000
Eating	.60 (.37)	.43 (.37)	.47 (.40)	1.196	.308	.002	.384	.862	1.000
Sensory Sensitivity	.36 (.32)	.35 (.35)	.38 (.30)	.045	.956	.003	1.000	1.000	1.000
COMPETENCE T	26.7 (8.9)	35.9(10.6)	20.8(10.6)	16.519	.000	.275	.012	.227	.000
COMPETENCE raw	.87 (.24)	1.04 (.31)	.72 (.27)	9.417	.000	.221	.177	.265	.000
Compliance	1.02 (.34)	1.09 (.32)	.95 (.41)	1.260	.289	.033	1.000	1.000	.350
Attention	.88 (.37)	1.08 (.47)	.88 (.53)	1.794	.173	.091	.454	1.000	.294
Mastery Motivation	1.18 (.43)	1.52 (.36)	1.12 (.40)	9.258	.000	.164	.012	1.000	.000
Imitation/Play	.77 (.43)	.98 (.48)	.65 (.46)	4.158	.019	.134	.337	1.000	.019
Empathy	.61 (.42)	.63 (.45)	.30 (.27)	5.643	.005	.232	1.000	.053	.006
Prosocial Peer Relations	.60 (.48)	.90 (.60)	.51 (.36)	3.731	.030	.105	.284	1.000	.033
ITEM CLUSTERS									
Maladaptive Item Cluster	.19 (.17)	.10 (.10)	.13 (.20)	1.701	.190	.025	.208	.811	1.000
Social Relatedness Item Cluster	1.27 (.33)	1.36 (.27)	1.28 (.32)	.836	.437	.006	.863	1.000	.861
Atypical Item Cluster	.79 (.48)	.61 (.39)	.67 (.39)	1.303	.278	.004	.332	.958	1.000

5.2.2 COMPARISON WITH A TYPICAL DEVELOPMENT GROUP

5.2.2.1 ITSEA: means comparison and accuracy (sensitivity and specificity)

Differences in mean ITSEA scores between the TD sample and the ASD samples were tested with independent samples T-tests, both for the overall groups and for the age subgroups. The mean scores in the overall groups are presented in Table 7, the ones in the subgroups are reported in Table 8. The comparison between ASD and TD overall groups shows strong significant differences in all the domains and item clusters, with the larger effect sizes in the overall Competence Domain, in the Depression/Withdrawal scale and in the Atypical Item cluster (η squared effect size of .498, .402 and .381, respectively). No significant differences in age were found across groups.

Table 7. T test between ASD and TD

	ASD (n=88)		% Of concern	TD (n=60)		% Of concern	Sig.	Effect Size
	M	SD		M	SD			
AGE	28.1	5.6		26.8	6.3		.197	.056
EXTERNALIZING T	49.5	12.2	9.4	44.3	7.4	1.7	.004	.008
EXTERNALIZING raw	.48	.31		.32	.20		.001	.025
Activity/Impulsivity	.70	.45	8.0	.41	.31	0	.000	.062
Aggression/Defiance	.46	.27	10.6	.36	.22	3.3	.019	.026
Peer Aggression	.15	.20	1.6	.19	.22	0	.264	.021
INTERNALIZING T	50.1	10.1	12.6	44.4	8.5	0	.000	.049
INTERNALIZING raw	.55	.22		.42	.18		.000	.047
Depression/Withdrawal	.35	.28	44.3	.04	.08	1.7	.000	.402
General Anxiety	.24	.20	8.2	.23	.19	5.0	.874	.001
Separation Distress	.92	.42	10.3	.71	.32	1.7	.001	.018
Inhibition to Novelty	.72	.47	3.8	.67	.43	3.3	.546	.000
DYSREGULATION T	47.0	13.6	11.4	38.9	8.4	0	.000	.043
DYSREGULATION raw	.52	.27		.33	.16		.000	.094
Negative Emotionality	.65	.37	19.3	.39	.25	1.7	.000	.077
Sleep	.45	.46	10.7	.41	.40	5.1	.547	.007
Eating	.48	.37	18.2	.26	.20	0	.000	.138
Sensory Sensitivity	.39	.35	11.6	.25	.22	0	.009	.031
COMPETENCE T	28.4	12.2	72.0	50.6	9.0	1.7	.000	.498
COMPETENCE raw	.88	.32		1.43	.27		.000	.426
Compliance	1.02	.36	37.9	1.32	.32	10.0	.000	.092
Attention	.96	.48	48.9	1.58	.39	1.7	.000	.298
Mastery Motivation	1.30	.43	39.5	1.67	.28	5.0	.000	.172
Imitation/Play	.80	.48	67.1	1.43	.31	11.7	.000	.350
Empathy	.50	.41	71.3	1.23	.47	8.6	.000	.400
Prosocial Peer Relations	.66	.52	56.7	1.31	.44	0	.000	.326
ITEM CLUSTERS								
Maladaptive Item Cluster	.15	. 19	28.0	.05	. 08	5.0	.000	.129
Social Relatedness Item Cluster	1.32	.30	55.7	1.61	.22	10.0	.000	.221
Atypical Item Cluster	.69	.41	55.7	.21	.25	3.3	.000	.381

When comparing the ASD and TD subgroups defined by the age under and above 24 months (Table 8), the two comparisons share significant differences in the Competence Domain, Depression/Withdrawal scale and all the Item Clusters (Maladaptive, Social Relatedness,

Atypical).In the subgroup under 24 months of age, a larger effect size can be observed for the Depression/Withdrawal scale, the Competence Domain, the Imitation/Play scale, The Social Relatedness and Atypical item clusters, in respect to the above 24 months subgroup. The older subgroup shows differences not seen in the younger group, in the Externalizing Domain (i.e. in the Activity/Impulsivity and in the Aggression /Defiance scales) and within the Internalizing domain, in the Separation Distress scale. In the older group strongest differences can be observed in the Dysregulation Domain and in the Negative Emotionality scale. It must to be noted that the mean scores in the Externalizing and Dysregulation domains and their scales are not in the "of concern" range.

Table 8 T test between ASD and TD under and above 24 months of age.

	ASD<24 (n=23)		TD<24 (n=17)		Sig.	Effect size	ASD>24 (n=65)		TD>24 (n=43)		Sig.	Effect Size
	M	SD	M	SD			M	SD	M	SD		
EXTERNALIZING T	47.6	10.0	45.4	7.9	.490	.019	50.9	12.6	43.9	7.25	.004	.013
EXTERNALIZING raw	.42	.31	.33	.20	.353	.009	.50	.31	.32	.20	.001	.034
Activity/Impulsivity	.67	.48	.40	.30	.047	.033	.71	.44	.41	.32	.000	.061
Aggression/Defiance	.35	.24	.43	.24	.295	.098	.49	.28	.33	.20	.001	.069
Peer Aggression	.15	.23	.13	.20	.734	.060	.15	.20	.22	.22	.115	.030
INTERNALIZING T	52.8	10.7	45.3	8.7	.024	.024	50.1	10.0	44.1	8.5	.002	.059
INTERNALIZING raw	.57	.24	.45	.17	.029	.41	.54	.21	.42	.18	.002	.049
Depression/Withdrawal	.45	.34	.02	.04	.000	.731	.31	.24	.05	.08	.000	.332
General Anxiety	.18	.12	.17	.15	.655	.021	.26	.22	.26	.20	.922	.000
Separation Distress	.96	.50	.82	.38	.327	.019	.91	.40	.67	.29	.001	.052
Inhibition to Novelty	.80	.45	.65	.40	.315	.000	.69	.47	.68	.44	.890	.000
DYSREGULATION T	48.0	12.5	41.3	8.4	.064	.046	46.7	14.0	38.0	8.3	.000	.049
DYSREGULATION raw	.52	.29	.35	.17	.040	.051	.52	.26	.32	.16	.000	.104
Negative Emotionality	.66	.33	.43	.25	.023	.035	.65	.38	.38	.25	.000	.089
Sleep	.48	.48	.62	.51	.389	.072	.44	.46	.32	.32	.142	.000
Eating	.40	.32	.16	.16	.007	.430	.51	.41	.30	.20	.002	.089
Sensory Sensitivity	.37	.32	.19	.14	.042	.171	.40	.36	.28	.24	.065	.013
COMPETENCE T	31.3	10.4	52.2	9.3	.000	.653	27.5	12.7	50.0	9.0	.000	.451
COMPETENCE raw	.77	.30	1.29	.32	.000	.540	.91	.32	1.48	.24	.000	.452
Compliance	.88	.33	1.19	.30	.004	.209	1.07	.36	1.37	.32	.000	.097
Attention	.99	.48	1.46	.42	.003	.344	.95	.49	1.63	.37	.000	.299
Mastery Motivation	1.42	.44	1.68	.33	.055	.157	1.26	.42	1.67	.27	.000	.174
Imitation/Play	.57	.45	1.43	.35	.000	.694	.87	.46	1.44	.30	.000	.296
Empathy	.30	.29	.94	.59	.000	.418	.56	.43	1.35	.38	.000	.469
Prosocial Peer Relations	.45	.37	1.03	.47	.002	.429	.72	.55	1.42	.39	.000	.370
ITEM CLUSTERS												
Maladaptive Item Cluster	.12	.15	.05	.07	.001	.077	.16	. 20	.04	.09	.000	.138
Social Relatedness Item Cluster	1.25	.30	1.63	.21	.000	.486	1.33	.29	1.61	.22	.000	.168
Atypical Item Cluster	.80	.37	.12	.11	.000	.722	.66	.42	.25	.28	.000	.303

The screening accuracy for the indices that have showed statistically significant differences and the higher effect sizes have been evaluated by calculating the Receiver Operating Characteristic (ROC) curves.

Namely the ROC curve has been calculated for the Competence Domain (Figure 9), the Depression/Withdrawal scale (Figure 10) and the Atypical Item cluster (Figure 11).

Sensitivity, specificity, positive and negative predictive values, have been calculated for these indices, with different cutpoints for the Competence Domain and for the Depression/Withdrawal scale (Table 9).

The AUC (95% confidence interval) of the Competence Domain was 0.918 (0.874-0.961), that of the Withdrawal/Depression scale was of 0.896 (0.844-0.947) and that of the Atypical item cluster was of 0.861 (0.800-0.921). The AUC of the Competence domain indicates high accuracy (AUC >0.90), while the AUCs of the Withdrawal/Depression and of the Atypical Cluster result in the moderate accuracy range ($0.70 \leq$ AUC <0.90). All the AUC's were significant (p=.000).

The AUCs (95% confidence interval) of these three indices were calculated for the age subgroups too. In the subgroup under the age of 24 months the AUC of the Competence Domain was 0.946 (0.875-1.000), that of the Withdrawal/Depression scale was of 0.941 (0.864-1.000) and that of the Atypical item cluster was of 0.985 (0.956-1.000). In the subgroup above the age of 24 months the AUC of the Competence Domain was 0.910 (0.857-.963), that of the Withdrawal/Depression scale was of 0.874 (0.807-.941) and that of the Atypical item cluster was of 0.811 (0.729-.893). All the AUC's were significant (p=.000)

Figure 9. ROC curve and AUC of the ITSEA Competence Domain

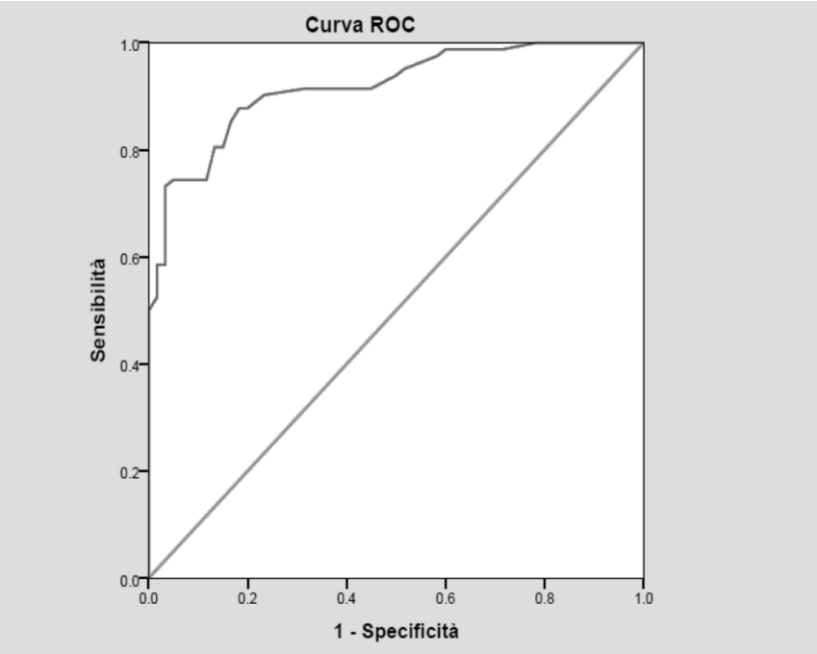
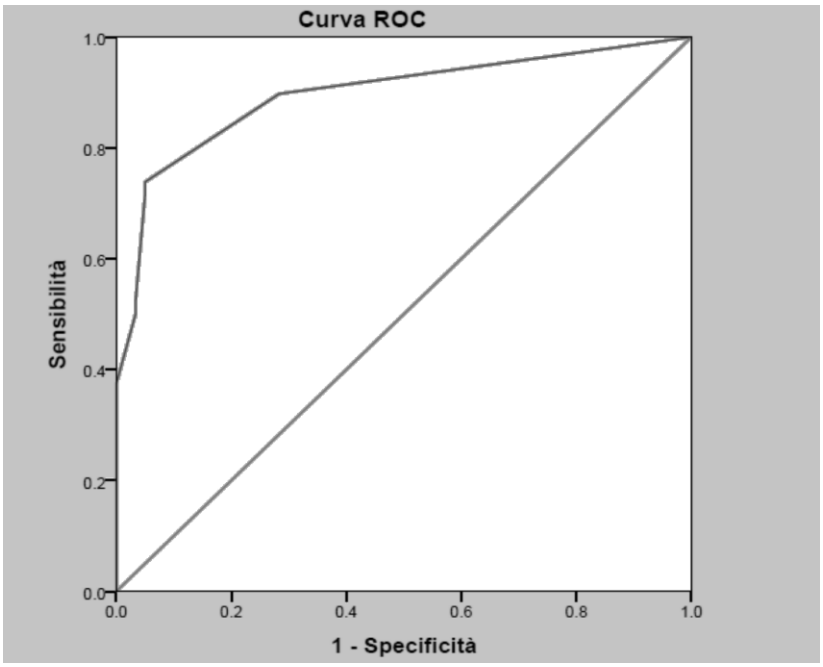


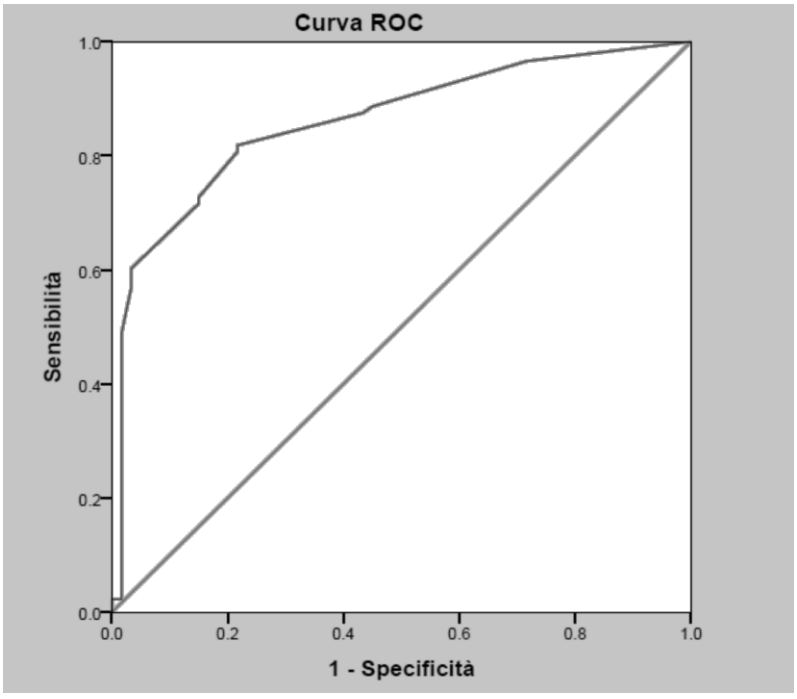
Figure 10. ROC curve and AUC of the ITSEA Depression/Withdrawal scale



AUC= .896

CI 95%= 0.844-0.947

Figure 11. ROC curve and AUC of the ITSEA Atypical Item Cluster



AUC=0 .861

CI 95%= 0.800-0.921

The Area under the Curve (AUC), sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV), both for the total sample and for subgroups by age, are reported in **Table 9.** Specifically are reported data for the Competence Domain and the Withdrawal /Depression at

different cut points (10th and 25th percentile), and for Atypical Item cluster at the 10th percentile of the normative distribution.

The Competence Domain shows the higher sensitivity and specificity: at the cut off corresponding to a T- score of 35 the sensitivity is of .72 with a specificity of .97; considering a T- score cut off of 42, which may approximate the cumulative percentage of 25 in the normative population (the correspondence for gender and age bands has been previously detailed), the sensitivity highs to .85, while the specificity lows to .81.

Both the Depression/Withdrawal and the Atypical Item Cluster show an excellent specificity, following Cicchetti et al. criteria (1995): specificity rates range from .97 to 1.00 in the total group and from .95 to 1.00 in the subgroups. However to those specificity rates correspond poor and fair (Cicchetti et al. 1995) sensitivity (ranging, in the total group and in the subgroups, from .39 to .61 for Depression/Withdrawal and from .48 to .78 for Atypical item cluster).

Considering a higher cut off corresponding to the 25th percentile, in the Depression/Withdrawal scale the sensitivity highs to .72 in the total group (.78 and .69 in the under and above 24 months, respectively), while the specificity lows to .93 in the total group and to .91 in age above 24 months group, remaining at a level of 1.00 in the age under 24 months group.

Table 9 Screening accuracy of ITSEA for the total sample and for subgroups by age

	AUC	Score	Se	Sp	PPV	NPV
COMPETENCE						
Total	**0.918 (0.874-0.961)**	**35**	.72	.97	.97	.72
		42	.85	.81	.90	.75
< 24 months	**0.946 (0.875-1.000)**	**35**	.63	1.00	1.00	.71
		42	.90	.88	.90	.88
> 24 months	**0.910 (0.857-.963)**	**35**	.75	.81	.86	.69
		42	.84	.97	.96	.85
DEPRESSION/WITHDRAWAL						
Total	**0.896 (0.844-0.947)**	**≤ 10°**	.44	1.00	1.00	.55
		≤25°	.72	.93	.94	.69
< 24 months	**0.941 (0.864-1.000)**	**≤ 10°**	.61	1.00	1.00	.65
		≤25°	.78	1.00	1.00	.77
> 24 months	**0.874 (0.807-.941)**	**≤ 10°**	.39	.98	.96	.51
		≤25°	.69	.91	.92	.66
ATYPICAL ITEM CLUSTER						
Total	**0.896 (0.844-0.947)**	**≤ 10°**	.56	.97	.97	.60
< 24 months	**0.941 (0.864-1.000)**	**≤ 10°**	.78	1.00	1.00	.77
> 24 months	**0.874 (0.807-0.941)**	**≤ 10°**	.48	.95	.94	.55

5.2.2.2 BITSEA: means comparison and accuracy (sensitivity and specificity)

In table 10 the child characteristics and the BITSEA Problem and Competence mean scores of Kruizinga et al. study and of our samples are reported.

Table 10.

BITSEA	ASD sample (Kruizinga et al.) N=159	Community sample (Kruizinga et al.) N=3127	ASD sample (Mottes et al.) N=88	TDsample (Mottes et al.) N=60
	Percentage (N)	**Percentage (N)**	**Percentage (N)**	**Percentage (N)**
Gender				
M	79.2(126)	50.9(1564)	84.1 (74)	71.7 (43)
F	20.8(33)	49.1(1535)	15.9 (14)	28.3 (17)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (months)	31.8(6.4)	23.7(0.7)	28.1 (6.0)	26.8 (6.3)
BITSEA Problem	20.5(8.7)	7.8(5.3)	12.2(6.6)	5.6(4.2)
BITSEA Competence	10.0(4.0)	17.5(3.0)	10.3(4.2)	16.0(3.8)

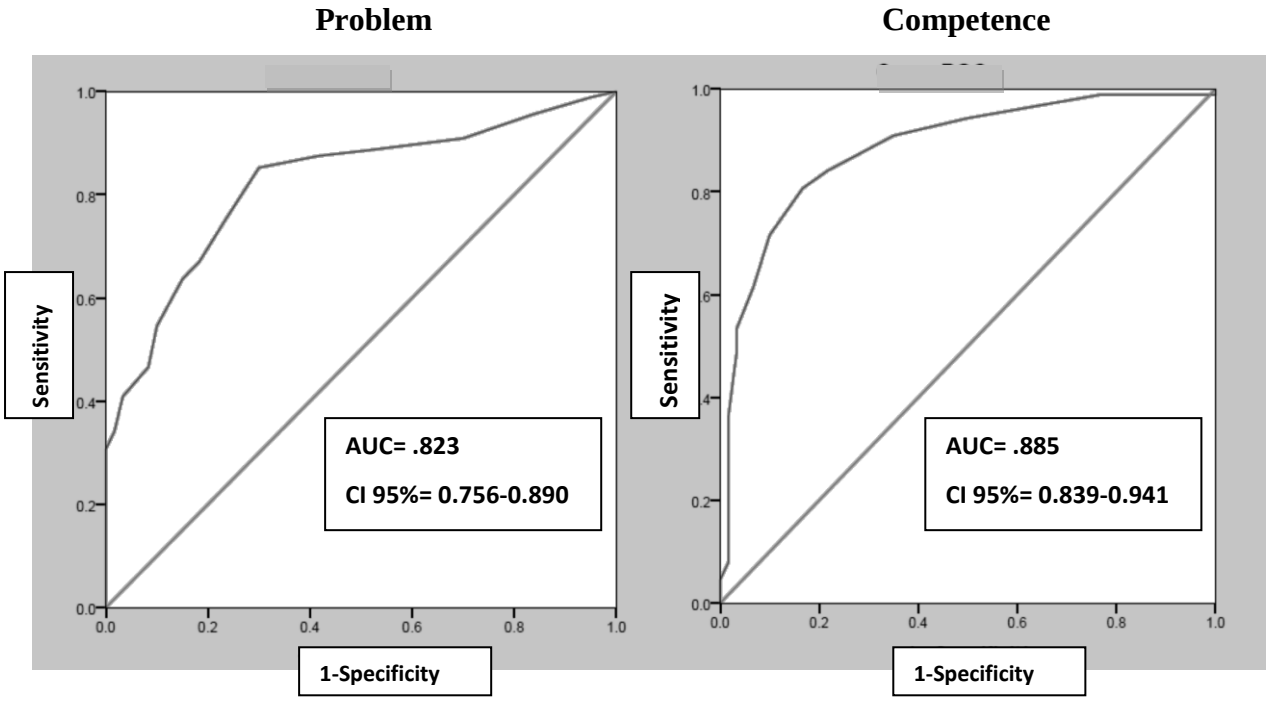
It must to be noted the large size of the Community sample inKruizinga et al. work (2014); this sample was recruited in the context of routine health examinations and it includes 2 years old children. While the mean Competence scores both in TD and ASD and the mean Problem score in TD of our samples are similar to that reported in Kruizinga et al.; the Problems mean score in our ASD sample appears lower in respect to that of ASD sample in Kruizinga et al.

The comparison (T test for independent sample) between ASD and TD in our samples has resulted statistically significant for both BITSEA Problem and BITSEA Competence (p=.000); effect size (Cohen's d) of 1.19 and 1.42, respectively.

ROC curves of the Problem and Competence scale scores are presented in Figure 12.

The AUC (95% confidence interval) of the Competence scale was 0.885 (0.839-0.941) and that of the Problem scale was of 0.823 (0.756-0.890), resulting in the moderate accuracy range ($0.70 \leq$ AUC <0.90). Both the AUC's were significant (p=.000).

Figure 12. ROC curve and AUC of the BITSEA Competence and Problem scales



In our sample we found for the Competence scale a sensitivity of .88 and a specificity of.77, while the Problem scale showed a sensitivity of .33 and a specificity of.97. For the Competence scale, considering the cutpoint of 15 proposed as the optimal cutpoint in Kruizinga et al. study, the sensitivity in our sample highs to .91, but the specificity lows to .65 (the sensitivity and specificity at the cut point of 15 in Kruizinga et. al are of .85 and .89 respectively). For the Problem scale, considering the cutpoint of 13 proposed as the optimal cutpoint in Kruizinga et al. study, the sensitivity in our sample reaches a value of .41, while the specificity remains of .97(the sensitivity and specificity at the cut point of 13 in Kruizinga et al. are of .83 and .84 respectively).

5.2.3COMPARISON WITH OTHER CLINICAL REFERRED GROUPS

In the last analysis performed we compared the ASD group with other clinically referred children (i.e. Developmental Delay and other Psychiatric Disorders).

5.2.3.1 COMPARSION WITH THE DEVELOPMENTAL DELAY GROUP

The comparison (ANOVA, Bonferroni post-hoc) between ASD, DD and TD showed significant ($p \leq .001$) differences in the Internalizing, Dysregulation and Competence domains, in the Activity/Impulsivity scale, within the Externalizing domain, and in all the Item Clusters. The Internalizing domain, the Depression/Withdrawal scale and the Atypical item cluster specifically differentiated the ASD group both from the TD and the DD group. The Dysregulation Domain and its scales differentiate ASD from TD, as previously observed, but they don't differentiate ASD from DD. The Competence Domain, the Maladaptive and Social Relatedness differentiate both the ASD and the DD from the TD group, but they don't differentiate between each other. No significant differences in age were found across groups. The results are reported in Table 13.

We then made a comparison between the same groups matched for age (ASD, DD and TD) and for developmental level (ASD and DD).

This comparison has confirmed significant differences, able to differentiate ASD group both from the TD and the DD group, for the Depression/Withdrawal scale and the Atypical item cluster.

The Competence Domain ($p=.000$) and the Maladaptive item cluster ($p=.002$) differentiate ASD and DD from TD; in this comparison the difference in the Social Relatedness mean score is statistically significant between ASD and TD, but not between DD and TD. The results are reported in Table 14.

ROC curves have been calculated for the indices showing a significant difference in the comparison between ASD and DD: the Depression/Withdrawal and the Atypical Item cluster. The AUC (95% confidence interval) of the Withdrawal/Depression scale was of 0.724 (0.613-0.834) and that of the Atypical item cluster was of 0.725 (0.608-0.841), resulting in the moderate accuracy range ($0.70 \leq$ AUC <0.90).All the AUC's were significant ($p=.000$).

5.2.3.2 COMPARSION WITH THE OTHER PSYCHIATRIC DISORDERS GROUP

The comparison (ANOVA, Bonferroni post-hoc) between ASD, OD and TD showed significant ($p \leq .001$) differences in the all the Domains and in all the Item Clusters. The Depression/Withdrawal scale, the Atypical item cluster and, within the competence Domain, the mastery Motivation, the Imitation/Play and the Empathy scale, specifically differentiated the ASD group both from the TD and the OPD group. The difference in the Aggression/Defiance scale resulted significant for the

OPD group (p=.000 and p=.01 in the comparison OPD vs TD and OPD vs ASD, respectively), while it wasn't significant in the comparison between ASD and TD. The differences in the competence Domain resulted significant (p≤.001) between the ASD and both the TD and OPD and between the OPD group and the TD group. No significant differences in age were found across groups. The results are reported in Table 15.

We then made a comparison between the same groups matched for age and for developmental level. This comparison has confirmed significant differences, able to differentiate ASD group both from the TD and the DD group, for the Depression/Withdrawal scale, the Atypical item cluster and the Empathy scale, even if the significance of the difference in the Depression/Withdrawal and Empathy subscale in the comparison between ASD and OPD resulted less strong (p= .034 and p=.021 respectively).

The difference in the Aggression/Defiance scale resulted significant for the OPD group (p=.000 and p=.01 in the comparison OPD vs TD and OPD vs ASD, respectively), while it wasn't significant in the comparison between ASD and TD. Significant differences, due to higher scores in the OPD group, were confirmed in the Externalizing Domain and its scales Activity/Impulsivity and Aggression/Defiance. Significantly higher scores in the OPD group resulted also in the Dysregulation Domain and in the Eating scale; within the Dysregulation domain the Negative Emotionality scores resulted higher in respect to TD group in both the ASD and the OPD group. The results are detailed in table 16.

ROC curves have been calculated for the indices showing a significant difference in the comparison between ASD and OPD (in the overall comparison or in the matched comparison): the Competence and the Externalizing domain, the Depression/Withdrawal scale and the Atypical Item cluster. Considering the overall comparison the AUC (95% confidence interval) of the Competence Domain was of Withdrawal/Depression scale was of 0.795 (0.710-0.880) and that of the Depression/Withdrawal scale was of 0.790 (.697-.883), the AUC of the Atypical item cluster was of 0.866 (0.801-0.931), and the AUC of the Externalizing Domain was of 0.748 (.627-.869), all resulting in the moderate accuracy range (0.70 ≤ AUC <0.90).All the AUC's were significant (p=.000).

In table 13, 14, 15 and 16 the green color highlights the significant differences which distinguish ASD from both the TD and the OPD/DD groups; the blue color highlights the significant differences that distinguish both the ASD and the OPD/DD groups from the TD group; the red color highlights the significant differences that distinguish the OPD/DD group from both the ASD and the TD groups.

Table 13. Comparison between ASD, DD and TD groups.

	ASD (n=88)		DD (n=24)		TD (n=60)		ANOVA Sig.	Effect size	Post Hoc ASD vs OPD vs TD		
	M	SD	M	SD	M	SD			ASD vs TD	ASD vs DD	DD vs TD
AGE	28.1	6.0	27.8	6.2	26.8	6.3	.428	.057	.592	1.000	1.000
EXTERNALIZING T	49.5	12.2	49.0	12.7	44.3	7.4	.016	.034	.016	1.000	.128
EXTERNALIZING raw	.48	.31	.42	..30	.32	.20	.003	.037	.002	.889	.516
Activity/Impulsivity	.70	.45	.70	.44	.41	.31	.000	.091	.000	1.000	.010
Aggression/Defiance	.46	.27	.44	.36	.36	.22	.080	.020	.084	1.000	.558
Peer Aggression	.15	.20	.11	.23	.19	.22	.253	.025	.813	1.000	.353
INTERNALIZING T	50.1	10.1	42.8	9.5	44.4	8.5	.000	.074	.000	.001	1.000
INTERNALIZING raw	.55	.22	.40	.18	.42	.18	.000	.064	.000	.008	1.000
Depression/Withdrawal	.35	.28	.16	.15	.04	.08	.000	.359	.000	.000	.069
General Anxiety	.24	.20	.16	.24	.23	.19	.208	.017	1.000	.251	.361
Separation Distress	.92	.42	.70	.28	.71	.32	.001	.028	.003	.027	1.000
Inhibition to Novelty	.72	.47	.53	.39	.67	.43	.208	.019	1.000	.231	.604
DYSREGULATION T	47.0	13.6	41.0	12.0	38.9	8.4	.000	.033	.000	.089	1.000
DYSREGULATION raw	.52	.27	.38	.22	.33	.16	.000	.078	.000	.031	1.000
Negative Emotionality	.65	.37	.57	.40	.39	.25	.000	.078	.000	.874	.088
Sleep	.45	.46	.29	.32	.41	.40	.265	.015	1.000	.314	.780
Eating	.48	.37	.36	33	.26	.20	.000	.113	.000	.294	.645
Sensory Sensitivity	.39	.35	.27	.26	.25	.22	.016	.047	.022	.211	1.000
COMPETENCE T	28.4	12.2	30.0	12.8	50.6	9.0	.000	.479	.000	1.000	.000
COMPETENCE raw	.88	.32	.89	.35	1.43	.27	.000	.424	.000	1.000	.000
Compliance	1.02	.36	1.03	.45	1.32	.32	.000	.121	.000	1.000	.003
Attention	.96	.48	.88	.44	1.58	.39	.000	.345	.000	1.000	.000
Mastery Motivation	1.30	.43	1.06	.51	1.67	.28	.000	.253	.000	.032	.000
Imitation/Play	.80	.48	.84	.40	1.43	.31	.000	.356	.000	1.000	.000
Empathy	.50	.41	.76	.54	1.23	.47	.000	.358	.000	.058	.000
Prosocial Peer Relations	.66	.52	.64	.46	1.31	.44	.000	.326	.000	1.000	.000
ITEM CLUSTERS											
Maladaptive Item Cluster	.15	. 19	.16	.17	.05	. 08	.000	.149	.000	1.000	.012
Social Relatedness Item Cluster	1.32	.30	1.44	.38	1.61	.22	.000	.181	.000	.175	.033
Atypical Item Cluster	.69	.41	.40	.33	.21	.25	.000	.330	.000	.001	.081

Table 14. Comparison between ASD, DD (matched for age and developmental level) and TD (matched for age)

	ASD (n=19)		DD (n=19)		TD (n=19)		ANOVA Sig.	Effect size	Post Hoc ASD vs OPD vs TD		
	M	SD	M	SD	M	SD			ASD vs TD	ASD vs DD	DD vs TD
AGE	29.8	5.0	29.6	5.2	29.6	5.0	.989	.076	1.000	1.000	1.000
EXTERNALIZING T	50.2	10.8	50.0	13.9	42.7	6.5	.060	.090	.114	1.000	.128
EXTERNALIZING raw	.51	.26	.44	.33	.31	.17	.073	.074	.076	1.000	.398
Activity/Impulsivity	.75	.42	.71	.46	.42	.27	.024	.153	.039	1.000	.073
Aggression/Defiance	.49	.25	.48	.40	.30	.17	.083	.088	.150	1.000	.173
Peer Aggression	.14	.16	.13	.26	.20	.22	.619	.016	1.000	1.000	1.000
INTERNALIZING T	50.8	9.6	43.3	9.5	45.6	8.7	.050	.041	.275	.052	1.000
INTERNALIZING raw	.53	.21	.41	.19	.43	.18	.144	.026	.395	.196	1.000
Depression/Withdrawal	.36	.23	.12	.11	.06	.08	.000	.290	.000	.000	.623
General Anxiety	.34	.28	.19	.26	.21	.15	.135	.149	.329	.196	1.000
Separation Distress	.79	.39	.69	.27	.73	.31	.619	.037	1.000	1.000	1.000
Inhibition to Novelty	.62	.41	.55	.42	.73	.42	.401	.066	1.000	1.000	.554
DYSREGULATION T	47.2	15.2	42.0	11.2	35.6	8.1	.016	.082	.013	.546	.330
DYSREGULATION raw	.59	.28	.40	.20	.29	.15	.002	.140	.002	.132	.363
Negative Emotionality	.55	.30	.58	.43	.34	.28	.074	.114	.180	1.000	.117
Sleep	.34	.37	.33	.34	.32	.37	.981	.046	1.000	1.000	1.000
Eating	.63	.39	.39	.35	.23	.19	.002	.130	.001	.087	.389
Sensory Sensitivity	.42	.35	.26	.23	.25	.21	.098	.062	.153	.222	1.000
COMPETENCE T	30.2	11.6	31.5	12.5	49.1	9.9	.000	.369	.000	1.000	.000
COMPETENCE raw	.95	.30	.94	.36	1.43	.25	.000	.382	.000	1.000	.000
Compliance	1.05	.34	1.08	.45	1.35	.32	.036	.115	.054	1.000	.114
Attention	.93	.41	.90	.45	1.60	.43	.000	.389	.000	1.000	.000
Mastery Motivation	1.38	.42	1.05	.52	1.62	.30	.001	.258	.260	.070	.000
Imitation/Play	.91	.41	.90	.41	1.44	.31	.000	.343	.000	1.000	.000
Empathy	.70	.41	.83	.55	1.25	.38	.002	.166	.002	1.000	.030
Prosocial Peer Relations	.77	.60	.68	.48	1.32	.38	.001	.308	.008	1.000	.001
ITEM CLUSTERS											
Maladaptive Item Cluster	.13	. 13	.14	.15	.02	.04	.002	.319	.008	1.000	.004
Social Relatedness Item Cluster	1.33	.24	1.44	.41	1.60	.21	.025	.121	.023	.904	.266
Atypical Item Cluster	.72	.41	.36	.28	.20	.21	.000	.301	.000	.003	.316

Table 15 Comparison between ASD, OPD and TD

	ASD (n=88)		OPD (n=27)		TD (n=60)		ANOVA Sig.	Effect size	Post Hoc ASD vs OPD vs TD		
	M	SD	M	SD	M	SD			ASD vs TD	ASD vs OPD	OPD vs TD
AGE	28.1	6.0	25.0	7.0	26.8	6.3	.070	.073	.622	.078	.676
EXTERNALIZING T	49.5	12.2	55.6	13.0	44.3	7.4	.000	.213	.017	.038	.000
EXTERNALIZING raw	.48	.31	.61	.33	.32	.20	.000	.198	.003	.113	.000
Activity/Impulsivity	.70	.45	.89	.56	.41	.31	.000	.176	.000	.143	.000
Aggression/Defiance	.46	.27	.63	.32	.36	.22	.000	.195	.073	.010	.000
Peer Aggression	.15	.20	.24	.33	.19	.22	.249	.033	.940	.330	1.000
INTERNALIZING T	50.1	10.1	48.5	10.5	44.4	8.5	.001	.053	.000	.867	.209
INTERNALIZING raw	.55	.22	.50	.22	.42	.18	.001	.054	.001	.838	.261
Depression/Withdrawal	.35	.28	.11	.14	.04	.08	.000	.376	.000	.000	.382
General Anxiety	.24	.20	.28	.22	.23	.19	.621	.007	1.000	1.000	1.000
Separation Distress	.92	.42	.89	.36	.71	.32	.004	.039	.003	1.000	.116
Inhibition to Novelty	.72	.47	.72	.56	.67	.43	.813	.011	1.000	1.000	1.000
DYSREGULATION T	47.0	13.6	55.1	16.8	38.9	8.4	.000	.246	.001	.011	.000
DYSREGULATION raw	.52	.27	.63	.31	.33	.16	.000	.236	.000	.109	.000
Negative Emotionality	.65	.37	.72	.40	.39	.25	.000	.156	.000	1.000	.000
Sleep	.45	.46	.67	.58	.41	.40	.043	.099	1.000	.096	.043
Eating	.48	.37	.76	.62	.26	.20	.000	.260	.002	.004	.000
Sensory Sensitivity	.39	.35	.35	.33	.25	.22	.033	.035	.028	1.000	.573
COMPETENCE T	28.4	12.2	41.0	9.6	50.6	9.0	.000	.464	.000	.000	.001
COMPETENCE raw	.88	.32	1.17	.25	1.43	.27	.000	.392	.000	.000	.000
Compliance	1.02	.36	.98	.30	1.32	.32	.000	.150	.000	1.000	.000
Attention	.96	.48	1.08	.50	1.58	.39	.000	.265	.000	.611	.000
Mastery Motivation	1.30	.43	1.59	.34	1.67	.28	.000	.169	.000	.002	1.000
Imitation/Play	.80	.48	1.31	.31	1.43	.31	.000	.330	.000	.000	.592
Empathy	.50	.41	1.07	.47	1.23	.47	.000	.356	.000	.000	.344
Prosocial Peer Relations	.66	.52	.84	.50	1.31	.44	.000	.290	.000	.441	.001
ITEM CLUSTERS											
Maladaptive Item Cluster	.15	. 19	.12	.12	.05	. 08	.000	.138	.000	1.000	.085
Social Relatedness Item Cluster	1.32	.30	1.42	.31	1.61	.22	.000	.185	.000	.201	.010
Atypical Item Cluster	.69	.41	.20	.18	.21	.25	.000	.395	.000	.000	1.000

Table 16 Comparison between ASD, OPD and TD matched for age and developmental level

	ASD (n=20)		OPD (n=20)		TD (n=20)		ANOVA Sig.	Effect size	Post Hoc		
	M	SD	M	SD	M	SD			ASD vs TD	ASD vs OPD	OPD vs TD
	25.5	6.8	25.5	6.9	25.4	6.8	.997	.047	1.000	1.000	1.000
EXTERNALIZING T	47.6	7.7	58.7	13.7	42.0	6.1	**.000**	.386	.249	.003	.000
EXTERNALIZING raw	.45	.22	.69	.34	.27	.15	**.000**	.368	.098	.011	.000
Activity/Impulsivity	.68	.39	1.03	.56	.36	.27	**.000**	.310	.075	.033	.000
Aggression/Defiance	.45	.21	.70	.32	.34	.22	**.000**	.281	.533	.009	.000
Peer Aggression	.16	.21	.26	.36	.12	.20	.269	.055	1.000	.941	.333
INTERNALIZING T	48.3	10.4	48.5	11.7	46.1	8.5	.724	.032	1.000	1.000	1.000
INTERNALIZING raw	.50	.23	.50	.24	.44	.17	.655	.036	1.000	1.000	1.000
Depression/Withdrawal	.30	.36	.11	.13	.05	.09	**.003**	.210	.003	.034	1.000
General Anxiety	.20	.14	.29	.25	.19	.17	.197	.067	1.000	.406	.320
Separation Distress	.97	.44	.89	.37	.83	.37	.556	.016	.850	1.000	1.000
Inhibition to Novelty	.65	.54	.70	.59	.70	.35	.928	.035	1.000	1.000	1.000
DYSREGULATION T	45.9	12.5	57.9	16.7	38.7	7.9	**.000**	.386	.240	.014	.000
DYSREGULATION raw	.51	.28	.69	.30	.33	.14	**.000**	.411	.084	.077	.000
Negative Emotionality	.64	.25	.79	.36	.37	.24	**.000**	.286	.022	.414	.000
Sleep	.44	.50	.82	.59	.42	.36	.025	.202	1.000	.066	.045
Eating	.40	.41	.82	64	.27	.21	**.001**	.322	1.000	.017	.001
Sensory Sensitivity	.38	.36	.34	.31	.26	.17	.396	.030	.570	1.000	1.000
COMPETENCE T	37.3	9.7	39.5	9.1	50.0	8.6	**.000**	.250	.000	1.000	.002
COMPETENCE raw	1.06	.32	1.12	.25	1.37	.27	**.003**	.147	.004	1.000	.023
Compliance	1.09	.37	.95	.34	1.30	.28	**.006**	.176	.184	.512	.004
Attention	1.15	.44	1.01	.52	1.58	.38	**.000**	.197	.011	.988	.001
Mastery Motivation	1.61	.24	163	.30	1.58	.30	.804	.015	1.000	1.000	1.000
Imitation/Play	1.02	.53	1.28	.32	1.40	.32	.010	.073	.009	.117	.965
Empathy	.61	.41	1.05	.52	1.13	.50	**.003**	.184	.005	.021	1.000
Prosocial Peer Relations	.86	.66	.81	.46	1.19	.46	.053	.109	.209	1.000	.072
ITEM CLUSTERS											
Maladaptive Item Cluster	.11	. 12	.13	.14	.03	. 06	.012	.208	.073	1.000	.016
Social Relatedness Item Cluster	1.36	.28	1.37	.32	1.59	.20	.015	.093	.027	1.000	.045
Atypical Item Cluster	.71	.45	.21	.19	.14	.17	**.000**	.405	.000	.000	1.000

5.2.3.3 COMPARISON WITH THE NON-ASD GROUP

We finally compared ASD group and the overall non-ASD group (DD plus OPD).

The results are reported in Table 11. No significant differences in age were found across groups.

Table 11.T test: ASD group vs non ASD group

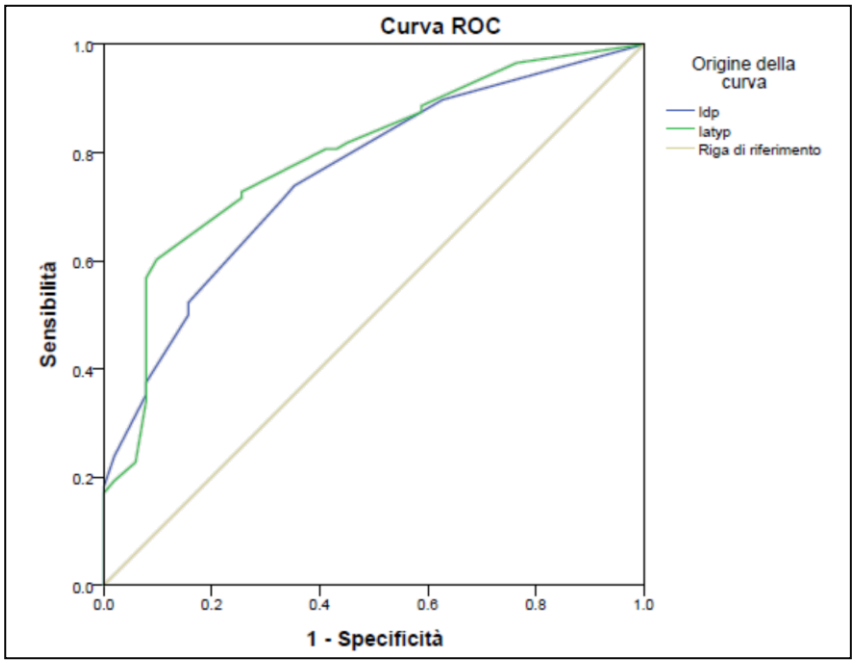
	ASD (n=88)		DD+OPD (n=51)		Sig.	Effect Size
	M	SD	M	SD		
AGE	28.1	6.0	26.4	6.7	.109	.096
EXTERNALIZING T	49.5	12.2	52.5	13.1	.180	.110
EXTERNALIZING raw	.48	.31	.52	.33	.492	.081
Activity/Impulsivity	.70	.45	.80	.51	.249	.067
Aggression/Defiance	.46	.27	.54	.35	.118	.048
Peer Aggression	.15	.20	.17	.29	.578	.012
INTERNALIZING T	50.1	10.1	45.8	10.3	.007	.016
INTERNALIZING raw	.55	.22	.45	.20	.016	.011
Depression/Withdrawal	.35	.28	.13	.14	**.000**	**.145**
General Anxiety	.24	.20	.22	.24	.647	.001
Separation Distress	.92	.42	.80	.33	.081	.000
Inhibition to Novelty	.72	.47	.63	.49	.338	.000
DYSREGULATION T	47.0	13.6	48.5	16.2	.549	.055
DYSREGULATION raw	.52	.27	.52	.30	.960	.026
Negative Emotionality	.65	.37	.65	.40	.959	.031
Sleep	.45	.46	.50	.51	.606	.042
Eating	.48	.37	.57	.54	.268	.027
Sensory Sensitivity	.39	.35	.31	.30	.168	.007
COMPETENCE T	28.4	12.2	35.7	12.4	**.001**	**.075**
COMPETENCE raw	.88	.32	1.03	.33	.008	.028
Compliance	1.02	.36	1.00	.37	.812	.036
Attention	.96	.48	.99	.48	.728	.002
Mastery Motivation	1.30	.43	1.34	.50	.605	.002
Imitation/Play	.80	.48	1.09	.43	**.000**	**.055**
Empathy	.50	.41	.92	.52	**.000**	**.152**
Prosocial Peer Relations	.66	.52	.74	.49	.437	.010
ITEM CLUSTERS						
Maladaptive Item Cluster	.15	. 19	.13	. 15	.635	.011
Social Relatedness Item Cluster	1.32	.30	1.43	.34	.034	.009
Atypical Item Cluster	.69	.41	.30	.20	**.000**	**.189**

The strongest significant differences ($p \leq .001$) were found for the Depression/Withdrawal scale, for the Atypical Item cluster, for the Competence Domain and, within the Competence Domain, for the Imitation/Play and Empathy scales. The higher effect sizes resulted for the Depression/Withdrawal scale, for the Atypical Item cluster and for the Empathy scale.

ROC curve has been calculated for the Competence Domain, the Depression/Withdrawal and Empathy scale and for the Atypical Item cluster. The AUC (95% confidence interval) of the Competence Domain was of 0.653 (0.578-0.769), that of the Withdrawal/Depression scale was of

0.757 (0.677-0.838), that of Empathy of 0.741 (0.655-0.828) and that of the Atypical item cluster was of 0.795 (0.719-0.871). The AUC of the Competence domain indicates low accuracy (0.50≤AUC<0.70), while the AUCs of the Withdrawal/Depression and of the Empathy scales and of the Atypical Item Cluster result in the moderate accuracy range (0.70 ≤ AUC <0.90). All the AUC's were significant (p=.000). ROC curve for the Withdrawal/Depression and of the Atypical Cluster are reported in Figure 13.

Fig.13 ROC curve and AUC of the scales Withdrawal/Depression and of the Atypical Cluster



Depression/Withdrawal

0.757 (0.677-0.838)

Atypical item cluster

0.795 (0.719-0.871)

For the same indices that showed the strongest statistic differences, sensitivity, specificity, positive and negative predictive values have been calculated, with different cut points for the Competence Domain, for the Depression/Withdrawal scale and for the Empathy scale. Results are reported in table 12.

Following Cicchetti et al. criteria (1995, the Competence Domain shows at the T-score cut off of 35, a fair sensitivity (.72), but a poor specificity (.54); when considering a T-score cut off of 42 the sensitivity highs to .85 (good) and the specificity lows to.35 (poor).

Both the Depression/Withdrawal and the Atypical Item Cluster show an excellent specificity (.91 and .92 respectively). However to those specificity rates correspond poor sensitivity rates (.44 and .56 respectively).

For what concern the empathy scale, at the 10th percentile cut off, the sensitivity is of.71 and the specificity is of .66.

Considering a higher cut off corresponding to the 25th percentile, in the Depression/Withdrawal scale the sensitivity highs to .72, while the specificity lows to .66, in the Empathy scale the sensitivity highs to .86, while the specificity lows to .49.

Table 12 Area Under the Curve (AUC), Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for Competence Domain, Withdrawal /Depression and Empathy at different cut points, for Atypical Item cluster at the 10th percentile

	AUC	Score	Se	Sp	PPV	NPV
Competence	**0.653 (0.578-0.769)**	**35**	.72	.54	.72	.54
		42	.85	.32	.67	.57
Depression/Withdrawal	**0.757 (0.677-0.838)**	**≤ 10°**	.44	.90	.89	.48
		≤15°	.59	.82	.85	.54
		≤25°	.72	.61	.76	.55
Empathy	**0.741 (0.655-0.828)**	**≤ 10°**	.71	.66	.78	.57
		≤15°	.81	.57	.77	.64
		≤25°	.86	.49	.74	.68
Atypical Item cluster	**0.795 (0.719-0.871)**	**≤ 10°**	.56	.92	.93	.55

The percentages of the "of concern" scores in all groups and subgroups are reported in table 17.

Table 17 Percentages of "of concern" scores in groups and subgroups

	% OF CONCERN								
	ASD	ASD <24	ASD > 24	TD	TD <24	TD > 24	DD	OPD	DD+OPD
EXTERNALIZING	9.4	4.8	10.9	1.7	5.9	0	8.3	22.2	15.7
Activity/Impulsivity	8.0	8.7	7.8	0	0	0	4.2	25.9	15.7
Aggression/Defiance	10.6	5.0	12.3	3.3	5.9	2.3	16.7	29.6	23.5
Peer Aggression	1.6	0	2.0	0	0	0	4.5	4.3	4.4
INTERNALIZING	12.6	18.2	10.8	0	0	0	0	3.7	2.0
Depression/Withdrawal	**44.3**	**60.9**	**38.5**	**1.7**	**0**	**2.3**	**4.2**	**7.4**	**5.9**
General Anxiety	8.2	0	10.9	5.0	0	7.0	4.3	7.4	6.0
Separation Distress	10.3	8.7	10.9	1.7	5.9	0	0	11.1	5.9
Inhibition to Novelty	3.8	5.3	3.4	3.3	5.9	2.3	0	14.8	7.8
DYSREGULATION	11.4	8.7	12.3	0	0	0	4.2	25.9	15.7
Negative Emotionality	19.3	26.1	16.9	1.7	5.9	0	8.3	25.9	17.6
Sleep	10.7	13.6	9.7	5.1	11.8	2.4	0	22.2	12.0
Eating	18.2	13.0	20.0	0	0	0	8.3	40.7	25.5
Sensory Sensitivity	11.6	9.5	12.3	0	0	0	4.2	7.4	5.9
COMPETENCE	**72.0**	**63.2**	**74.6**	**1.7**	**0**	**2.3**	**62.5**	**30.8**	**46.0**
Compliance	37.9		33.8	10.0	0	14.0	37.5	29.6	33.3
Attention	48.9	43.5	50.8	1.7	0	2.3	37.5	37.1	37.3
Mastery Motivation	39.5	28.6	43.1	5.0	5.9	4.7	58.3	11.1	33.3
Imitation/Play	**67.1**	**89.5**	**61.5**	**11.7**	**0**	**16.3**	**66.7**	**14.8**	**39.2**
Empathy	**71.3**	**70.6**	**71.4**	**8.6**	**18.8**	**4.8**	**47.8**	**20.0**	**34.0**
Prosocial Peer Relations	**56.7**	**41.7**	**60.4**	**0**	**0**	**0**	**57.1**	**30.4**	**43.2**
ITEM CLUSTERS									
Maladaptive Item Cluster	28.0	26.3	28.6	5.0	0	7.0	34.8	18.5	26.0
Social Relatedness Item Cluster	**55.7**	**73.9**	**49.2**	**10.0**	**5.9**	**11.6**	**29.2**	**33.3**	**31.4**
Atypical Item Cluster	**55.7**	**78.3**	**47.7**	**3.3**	**0**	**4.7**	**20.8**	**0**	**9.8**

Chapter 6

Discussion and Conclusions

Clinical tools able to characterize and identify young children with Autism Spectrum Disorder are strongly needed to increase our knowledge at the early presentation of this disorder and, as a consequence, to improve our capacity of detection in its first beginning, in order to guide the research in the investigation of the etiological, neurobiological and neuropsychological underpinning of ASD, as well as to promote the individualization of the treatment approach.

The ITSEA is specifically developed for infants and toddlers (12-36 months). It can be considered a broadband instrument, directed to a comprehensive evaluation of the social and emotional development (including externalizing and internalizing symptoms, aspects regarding the "regulatory system" and competencies), and not only directed to identify the "red flags" of autism. This characteristic appears relevant to better characterize the early expression of autism as well as identify difficulties that, even if not confirming a disturb, may co-occur influencing the development. As profusely reported in the ITSEA Manual, a questionnaire cannot substitute the clinical assessment and the direct recollection of information from parents, however it could be helpful to highlight aspects that are source of concern for parents and that could not immediately emerge during a time-limited assessment. Surely, information about frequency, intensity, timing, context and parent's perception of the problematic behavior or deficit, together with a comprehensive clinical assessment, are necessary to contextualize the "of concern" dimensions highlighted by the ITSEA.

In our study we have taken in consideration the use of ITSEA in a population of children with ASD. The first aim of this study was to examine if the ITSEA could provide a recognizable profile in toddlers with a diagnosis of Autism Spectrum Disorder, as proposed in the ITSEA Manual.

ITSEA profile in the overall Autism Spectrum Disorder sample (ASD): comparison with the Manual Autistic Disorder sample (AD)

As expected the profile in our ASD sample was similar to the one proposed in the Manual, with mean scores in the "of concern" range for those indices, hypothesized to address autism core symptoms (namely, the Depression/Withdrawal scale, the Social Relatedness and Atypical Item clusters, the Competence Domain, within which in particular, the Imitation/Play, the Empathy and

the Prosocial Peer relation scales) (Table 1-Chapter 5). Moreover the ITSEA could identify a percentage of clinical scores in other areas as like externalizing (Activity/Impulsivity, Aggression Defiance scales) and internalizing (Separation Distress scale) symptoms and symptoms addressed in the Dysregulation domain. In the last one, are included items referred to the capacity to modulate the negative emotional response, eating problems and difficulties concerning the reactivity to sensory stimuli. In all these areas there weren't "of concern" mean scores, but the percentages of "of concern" scores in the ASD sample resulted higher than what observed in the Typical Development sample.

Even if the mean score profile in our sample resulted similar to the Manual AD profile, the prevalence of "of concern" scores (i.e. the scores below the 10^{th} percentile of the normative population) in our sample has resulted lower (Table 1-Chapter 5). To explain this difference, it has to be considered that the Manual AD group was including children aged 18-35 months, with a diagnosis of Autistic Disorder, while children with a Pervasive Developmental Disorder not otherwise specified were excluded. Instead our sample is comprised of children still not diagnosed at the time that their parents completed the questionnaire and the diagnostic inclusion criteria is a diagnosis of Autism Spectrum Disorder in which children who would have previously been diagnosed as PDD-NOS, in relation to a milder expression of symptoms, can be included.

Moreover, considering the frequency distribution of the scores within the classes (Figure 2 and 3-Chapter 5), we can observe that the prevalence of scores rapidly grow within the 15^{th} and 25^{th} percentile, almost reaching and sometimes exceeding the prevalence of scores at the 10^{th} percentile of the Manual's sample . This observation suggests that the distribution of the scores in our sample differs from the one in the normative population, even if our sample has a wider distribution of the scores within the 25^{th} percentile and not within the 10^{th} percentile.

The greatest difference within the Domains scores is relative to the Dysregulation domain. This is relevant considering the recent inclusion of the sensory responsiveness (hyper- or hypo reactivity) to sensory input and unusual interest in sensory aspects of the environment criteria in the ASD diagnosis of the DSM-5 (DSM-5, 2012).

Studies concerning sensory responsiveness in ASD have highlighted that persons with ASD tend to show more than one type of Sensory Modulation Disorder, often showing a combination of hypo and hyper-responsiveness to sensory stimuli with a prevalence of hypo-responsiveness in particular during early childhood (Rogers &Ozonoff, 2005; Ben-Sasson et al., 2009; Baranek et al., 2013); a trajectory characterized by an increase in the frequency of sensory behaviors overall, in over-responsivity and in seeking up to age 6–9 years, and a decrease there after has been reported (Ben-Sasson et al., 2009). The ITSEA Dysregulation Domain is comprised of scales that measure

Sleeping and Eating problems, Negative emotionality and Sensory sensitivity. The items of the Sensory sensitivity scale overlap the manifestations of over-responsivity; however in a previous work (Green et al., 2012) it is suggested that this scale may underestimate sensory over-responsivety (SOR), given the previously detection of a higher prevalence of SOR in the same group of children using another tool (i.e. the ITSP). Moreover, in consideration of the previous reported data on co-occurrence of hypo-, hyper-responsivety and seeking behaviors, and the trajectory of emergence of sensory symptoms, it is possible that the Sensory sensitivity scale of ITSEA doesn't cover the landscape of sensory manifestations in autism, especially in the younger age. In a previous study (Maestro et al., 2012.), we examined the phenotypic expression of the Regulation Disorders of Sensory Processing (DC: 0-3) through the data provided by the clinical assessment tools. The outcome showed that parents reports (i.e. ITSEA) seemed to be more sensitive in detecting the effects of the sensory processing disturb through the emotional and behavioral indices intercepted by the scales in the Externalizing domain and in the Negative Emotionality scale of the Dysregulation domain. Moreover in Carter et al. (2003) the evaluator ratings of Dysregulation correlated significantly with ITSEA reports of problems in all the domains and, conversely, ITSEA Dysregulation correlated with evaluator reatings of Externalizing and Internalizing problems.

Ben-Sassoon et al. (2008) examined the relation between the sensory and the affective symptoms in toddlers with ASD using the ITSEA Negative emotionality and Internalizing scales as measures of the affective symptoms. They reported that children with overall higher sensory symptoms (under, over-responsivity and seeking) differed from children with low sensory symptoms showing significantly higher mean scores in the anxiety and separation distress, but in particular in the Depression/Withdrawal scale, even when ASD-specific items were excluded, and in the Negative emotionality scale. Those findings suggest the need to assess possible associated affective symptoms in children who show sensory symptoms; they also support the idea that behavioral and emotional symptoms, such as that detected by the negative emotionality scale and the depression/withdrawal scale, should be indicative of a more complex impairment of the "regulatory system" that could otherwise remain undetected.

ITSEA profile in the Autism Spectrum Disorder subgroups defined by age

In the comparison between the ASD subgroups defined by age below and above 24 months, we unexpectedly found higher percentages of "of concern" scores (Table 5-Chapter 5) in the scales addressed to ASD symptoms in the younger group. In particular higher percentages were found in the Depression/Withdrawal and Imitation/Play scales and in the Social Relatedness and Atypical

item clusters. (The items composing these scales are reported at the end of the chapter). These data suggest that the ITSEA may be more sensitive in detecting ASD symptoms in the early age comprised between 12 and 23 month in respect to children aged 24 to 36 months. The hypothesis is supported by the frequency distribution of the scores (i.e. Depression/Withdrawal scale and the Imitation/Play scale; Figures 5 and 7-Chapter 5) and by the larger effect size of the differences between ASD and TD children under the age of 24 months, in respect to the same comparison within the older children (Table 8-Chapter 5); moreover an higher accuracy in the younger subgroup has been demonstrated by the analysis with the ROC curves whose AUCs in the Depression/Withdrawal scale, in the Atypical Item cluster and in the Competence were found to be larger in the young group. This is consistent with the findings of our previous study (Narzisi et al.) where the sensitivity and specificity of Withdrawn and PDP scales of the CBCL in a toddlers sample resulted better compared to previous results in an ASD preschoolers group. It is important to consider that in that case the toddler group mean age was of 29.4 months and the preschooler mean age was of 44 months, while in our sample the young group mean age is 19.7 months and the older group mean age is 31.1 months; however the hypothesis of a tendency to more evident symptoms of withdrawal and other ASD symptoms in the younger ages is confirmed. In our previous work two possible explanations have been hypothesized: first the habituation to autistic behaviors of parents of the older children and, second, the possibility that CBCL items may be more appropriate for children aged 2-3 years. Considering the items included in the ITSEA ASD addressed scales (especially Social Relatedness, Atypical item cluster, Depression/Withdrawal), we may hypothesize that ITSEA should be particularly sensitive to detect symptoms such as anomalous eye contact, lack of response to name, lack of pointing and reduced positive affect, which studies have highlighted as red flags of ASD, during the second year of life (Wetherby et al., 2004; see Zwaigenbaum et al., 2013 for a review). The same symptoms could be less evident in older children, especially in case of a milder severity. Indeed we can observe that the older group cumulated percentages of scores at the 15th and the 25th percentile reach those of the younger group at the 10^{th} percentile. Two possible explanations can be suggested: either the older group is milder affected or these scales items are more sensitive in detecting ASD manifestations typical of children younger than 24 months. Looking at the distribution of "of concern" percentages (Table 5-Chapter 5), in the older group we can instead observe higher percentages in more advanced competencies as like Mastery motivation and Prosocial peer relation and a higher percentage of global impairment in the Competence Domain (74.6% older group vs. 63.2% younger group). A higher "of concern" prevalence, even if not resulting in a mean "of concern" score, can be observed also in the

Externalizing domain, in particular in the Aggression/Defiance scale, while we found the inverse tendency in the Typical development group (Table 17-Chapter 5).

ITSEA profile in the Autism Spectrum Disorder subgroups defined by gender

In the comparison between girls and boys within the overall ASD sample we found a significant difference relative to the Competence domain, due to a lower mean score in the female subgroup; there were no sex differences in any of the ITSEA problem domains (Internalizing, Externalizing, and Dysregulation). These findings were confirmed when comparing two age and developmental matched female and male groups and are consistent with the results of Carter et al. (2007). We also found in the female group a higher prevalence of "of concern" scores in the Depression/Withdrawal. The finding of a more severe impairment could be considered consistent with literature data reporting a possible gender diagnostic bias. Indeed, as highlighted in a recent review (Lai et al.) empirical data suggest high-functioning females are diagnosed
Later than males and indicate a diagnostic bias towards males; females need more con current behavioral or cognitive problems than males do to be clinically diagnosed.

ITSEA profile in the Autism Spectrum Disorder subgroups defined by developmental level

The correlations between the ITSEA domains and the results of standardized developmental assessments have been examined both in non-clinical and clinical groups (Carter et al. 2003; Carter and Briggs-Gowan, 2006). The findings suggested a confirmation of the developmental nature of the Competence domain (increase of competencies with developmental level), but the levels of associations between ITSEA Competence and the developmental levels didn't result strong enough to suggest they were measuring the same construct. In our study, the results of the comparison between the two groups with different developmental levels and the non-assessable group, within the ASD group, seems to give confirmation to those findings. Indeed we found higher mean scores in the overall Competence domain and scales in the higher developmental level group than the lower one. However the strongest differences have resulted in the comparison between the higher developmental level group and the non-assessable group, suggesting that the Competence domain measures aspects of adaptability that are not only dependent on developmental level. We must however consider, as other possible explanation, that the non-assessable group may be comprised of children with a more severe impairment relative to the developmental level.

Besides to define the ITSEA ASD profile, we wanted to preliminarily examine the capacity of ITSEA to discriminate between ASD and both the typical development and other clinical referred children.

Comparison with a Typical Development group

The identification of adequate tools to detect children at risk of autism in primary care is crucial for secondary prevention and to reduce the time gap between the first parents concerns and the first diagnosis that is still reported in literature (Wiggins et al. 2006; Barbaro & Dissanayake, 2009; Daniels et al., 2013).

As summarized in Briggs-Gowan et al. (2004) a screening tool should have all the subsequent characteristics: to be brief and easy to administer, score, and interpret; to have adequate reliability and validity and identify an acceptable percentage (a minimum of 70%) of children who have problems, yet have a false-positive rate of no greater than 30%; to provide developmentally appropriate and clinically useful information .

ITSEA

In our sample we found that the most accurate index in discriminating ASD children from Typical development children is the Competence Domain which has demonstrated, according to Cicchetti et al. criteria (1995), a high accuracy (AUC= 0.918; CI 95%0.874-0.961)and good sensitivity (.85) and specificity (.81) using the cut-off of 42 that we can consider to approximate the 25th percentile of the normative population for all gender and age bands of the ITSEA. These values of specificity and sensitivity are above .80, which is the recommended cut-off for first-level screening instruments. The competence domain is followed, for what concerns discriminative accuracy, by the Depression/Withdrawal scale and the Atypical Item cluster (see Table 9). These indices showed a poor sensitivity, considering the overall ASD group, but an excellent specificity (ranging from .97 to 1.00). When considering the cut-off point at the 25th percentile instead of the 10th percentile, the sensitivity of the Depression/Withdrawal scale increase to a fair level, maintaining an excellent specificity. The same evaluation hasn't been made for the Atypical item cluster, for whom percentile distribution are not available, but this index has shown in the younger group fair to good sensitivity and excellent sensitivity. Based on these results we should hypothesize that at a primary level screening, a low score (below a T-score of 42) in the Competence domain of the ITSEA may suggest the suspicious of ASD, which should be reinforced by associated "of concern" values in the Atypical item cluster, low percentiles (below 25th percentile) in the Depression/Withdrawal scale

and a pattern of Competence characterized by a particular impairment in Imitation/Play, Empathy and Prosocial Peer relation.

BITSEA

The brief version of the ITSEA has been thought to address the need of a measure sensitive to social emotional/behavioral problems, autism spectrum disorders, and delays in social-emotional competence in early childhood (12-36 months). As the ITSEA, the BITSEA presents the advantage to measure competencies, which is important since delays in acquiring social-emotional abilities may be a risk factor for the acquisition of new developmental demands and for social and emotional problems (Bornstein, 2010).

At the same time BITSEA is a short parent-report measure whose completion require 5-7 minutes, therefore it presents the characteristics of shortness, easiness of administration, score and interpretation that are warranted for a screening instrument. In a previous study where BITSEA application in a clinical referred population and in comparison with a community sample have been examined (Karabekiroglu et al. 2010), were found significant lowers BITSEA Competence scores in the autism group (n= 35 maternal BITSEA/C= 9.32 ± 3.53) in respect to a community sample (n= 427 maternal BITSEA/C= 15.61 ± 3.81). In the already cited (see chapter 5.3.2) study of Kruizinga et al. (2014) both the BITSEA Problem and the BITSEA Competence have shown a good screening accuracy with regard to ASD. Our results are consistent with the low BITSEA Competence score found in both the cited studies and has demonstrated a good sensitivity (.88) and a fair specificity (.77); instead the mean score of the BITSEA Problem, even if significantly different from the mean score of the Community sample, has resulted lower in respect to that reported in the previous papers, and has shown excellent specificity (.97), but a low sensitivity. These results appear consistent with the discussed results concerning ITSEA, where the Competence Domain has been found to be the most accurate index.

Certainly, as in many of the proposed screening instruments, confirmation of these results need to be find in the replication with larger size samples and the analysis of the screening validity for ITSEA needs the application in a large community sample, with adequate follow-up of screened-negative cases (Garcia-Primo et al., 2014). In respect to the other available screening measures ITSEA and BITSEA present some advantages: they evaluate both problems and competencies, whose relevance has been discussed above; they are applicable to children since the age of 12 months, age that, within the parent-report level 1 instruments, is addressed by few instruments (i.e. the First Year Inventory, the Communication and Symbolic Behavior Scales-Developmental Profile).

Comparison with other clinical referred groups

In the last part of our study we examined the comparison between clinical referred groups. As suggested by Myers et al. (2013), it is important to provide tools able to support the clinical assessment and the differential diagnosis process. Tools able to support a comprehensive multidimensional information about early social-emotional development can help in the detection of possible problems or deficits, promoting the identification of all the areas in which intervention is warranted as well as, by assessing competencies, of the strength areas that should be of support in the intervention program (Briggs-Gowan& Carter, 2007). Parents constitute, relatively to their child development, a unique source of information. The relevance of this information source is also supported by the evidence of reliability (Glascoe, 2003). Moreover parent-report instruments are easy to administer, inexpensive, repeatable in order to monitor treatment effectiveness (Carter, Briggs-Gowan, & Davis, 2004); additionally this kind of tools uses an objective scoring procedure that is intended to minimize social worker subjectivity or bias and does not require any type of specialized training or special setting or materials. For all these reasons is important to identify reliable and valid parent-report tools to support not only the screening level, but also the clinical assessment level.

In the comparison with the non-ASD clinical group, the Depression/Withdrawal scale and the Atypical Cluster, the Competence Domain, in particular, the Imitation/Play and the Empathy scale, confirmed to highlight more differences. However, in this case, the Competence domain hasn't showed an adequate accuracy in discriminating between the two groups (sensitivity of .72, and specificity of .53 at the cutoff of 35, sensitivity of .85, and specificity of .32 at the cutoff of 42). This doesn't surprise since the competences are not specifically addressed to the ASD symptoms; in the comparison with the Other Mental Health Problems group and with the Developmental Delay group proposed in the ITSEA Manual both the groups were expected to have, and showed, lower mean scores in the Competence domain and scales in respect to a control matched group. Our results, considering the overall non-ASD group, as well as the Developmental Delay and the Other Mental Health Problems groups separately, confirm this expectation. A pattern of Competence impairment characterized by a greater impairment in scales such as Empathy and Imitation/Play may be indicative of ASD in the comparison with other mental health problems (Se .71 and .67 and Sp .80 and .85, respectively), but not in the comparison with the developmental delay.

The Atypical item cluster and the Depression/Withdrawal scale confirm their high specificity (.91 and .92 respectively) for ASD, but low sensitivity (.44 and .56). Considering different cut off for the Withdrawal/Depression scale, the Sensitivity goes to .59 and .72 at the 15^{th} and 25^{th} percentile, while the correspondent specificities drop down to .82 and .61, respectively.

The Dysregulation domain has shown differences between clinical and Typical development groups, but it doesn't discriminate between different diagnosis within the clinical referred group. Consistent with our previous data in a group of children with a diagnosis of Regulatory Disorder of Sensory Processing (Maestro et al. 2012), the mean scores of Externalizing Domain in our Other Psychiatric Disorders sample resulted higher than both the TD and ASD. This is not surprising considering that, as previously suggested in this discussion and as highlighted by Visser et al. (2010), in early problems of the emergent self-regulatory system there is an interplay of sensory processing, emotional and behavioral regulatory difficulties associated with both internalizing and externalizing manifestations. The system of regulation exactly plays its role at the interface between the interior processing of sensory inputs and the organization of the exterior response (Dale, 2011)
Moreover Regulatory Disorders have been associated with various disorders at older ages, concerning both externalizing and internalizing dimensions (De Gangi et al. 2000; Maestro et al., 2012).

Limitations and perspectives

First of all the translation of the ITSEA is a forward translation only; even if we used a committee approach and the final translation is the result of a consensus between two independent groups, a back translation process is requested to improve the validity of the Italian version.
Second, as long as there are not normative data for the Italian population, the normative data used in this paper refer to the USA population
Third, the children of our sample were recruited from referred and non-referred sources to obtain a sufficient number of children with disorders to test study aims; this design may influence generalizability because the prevalence of a problem affects PPV, with PPV decreasing as prevalence decreases.
Moreover to define the accuracy of a tool as screening tool, the application in a large community sample with adequate follow-up of the screened negative cases is warranted.
On the other side the big advantage of ITSEA and BITSEA is that they are addressed to children under 12 months of age. A larger sample of children under 18 months should be analyzed.
In our study we didn't perform comparison between ITSEA and other clinical indices that define the ASD phenotype, except for the developmental level. In prospective it would be useful to better evaluate these correlations in order to examine if ITSEA can identify subgroups defined by the phenotype.
A future perspective could be the analysis of the scales and items found to address ASD symptoms in order to eventually identify a specific ASD cluster of items.

Conclusions

The primary aim of our study was to examine the ITSEA profile in ASD toddlers with Autism Spectrum Disorder and, secondary, to analyze its capacity to discriminate ASD toddlers from both Typical development and others developmental/mental health problems. To our knowledge previous literature data concerning the ITSEA profile in ASD and its validity in discriminate between different clinical conditions are referred to smaller samples of ASD (Carter and Briggs-Gowan, 2006; Visser et al. 2007) or they are not primarily aimed to the identification of an ITSEA profile indicative of ASD (see Table 1 in Chapter 4).

Our results suggest a good capacity of the ITSEA to identify a condition of developmental concern through its Competence domain and the possibility to point to a suspicion of ASD through its specific, even if less sensitive, indices and patterns of Competence's impairment. Due to its broad developmental approach, capable to address temperamental indices and developmental aspects of social-emotional competencies, ITSEA seems to adequately follow the theoretical approach to Autism Spectrum Disorder as a neurodevelopment disorder involving multiple developmental domains and resulting, through a vulnerability and cascade model, in the typical manifestations of social and communicative impairment and restrictive and repetitive behaviors. (Rogers et al. 2009; Zwaigenbaum et al. 2013). For what concerns the aim of distinguish between children with ASD and other referred children, we couldn't identify a singular index that individually discriminate children with ASD. However, as proposed by Visser et al. (2007), we can identify patterns of profile that are highly suggestive of ASD or of other clinical conditions. Moreover in its clinical application ITSEA can constitute a supportive tool for a comprehensive assessment of the social and emotional development, necessary to warrantee the identification of all areas of problem as well as, thanks to its competence domain, of strengths.

Replications of our results and the application to larger community samples are needed to confirm and improve the findings.

ITSEA scales and items addressed to Autism Spectrum Disorder symptoms

Depression/WithdrawalSubscale
Has less fun than other children
Does not make eye contact
Avoids physical contact
Laughs easily or a lot
Looks unhappy or sad without any reason
Feels bad about himself or herself
Seems to have no energy
Seems withdrawn
Seems very unhappy, sad or depressed
EmpathySubscale
Tries to help when someone is hurt (for example, gives a toy)
Tries to make you feel better when you're upset
Worried or upset when someone is hurt
Tries to "make-up" for misbehaving
Aware of other people's feelings
Jokes or gives you things to make you smile or laugh
Talks about other people's feelings (for example, "Mommy mad")
Imitation/Play Subscale
Imitates playful sounds when you ask him or her to
Hugs or feeds dolls or stuffed animals
Rolls a ball back to you (or someone else)
Pretends to do grown-up things, like shaving
Pretends that objects are something else (for example, uses a banana as a phone)
Imitates clapping or waving bye-bye
Prosocial Peer Relations Subscale
Plays well with other children (not including brother or sister)
Takes turns when playing with others
Asks for things nicely when playing with other children
Has at least one favorite friend (a child)
Plays house with other children
Social Relatedness Item Cluster
Looks for you (or other parent) when upset
Looks right at you when you say his or her name
Affectionate with lovedones
Responds the first time his or her name is called
Hugs people with a squeeze or a pat
Likes being cuddled, hugged, or kissed by loved ones
Reaches for you when you are not holding him or her
Prefers you (or other parent) over other adults
Interested in babies and children
Smiles back at you from across a room
Atypical Item Cluster
Points to show you something far away
Puts things in a special order over and over and gets upset if he or she is interrupted
Repeats the same action or phrase over and over without enjoyment
Repeats a particular movement over and over (like rocking or spinning)
Spaces out. Is totally unaware of what's happening around him or her
Points to ask for something
Without looking at you, puts your hand on objects, such as wind-up toys, to make them work
Hasvery strange habits

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