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Estimating cognitive functioning in Autism Spectrum Disorders: a longitudinal study from developmental profile to IQ level.

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Abstract

Over the last decade or more, besides an increased prevalence of autism diagnoses, the rate of associated Intellectual Disability (ID) tended to decrease. Among Autism Spectrum Disorders (ASDs), IQ was found to be a strong predictor of short- and long-term outcomes, such as a potential moderator of response to treatment strategies. Thus, a specific assessment of cognitive functioning, as soon as possible, should be rigorously performed to obtain an appropriate evaluation of ASD subjects. Unfortunately, in the clinical practice, administering IQ tests can be difficult and potentially result in lower scores due to the typical clinical phenotype and behavioral problems. In young ASD children, the Psychoeducational Profile-3 (PEP-3) represents the most useful and manageable tool for the assessment. Building on existing literature, although most studies to date have been cross-sectional, PEP scores were found to be related to IQ levels; thus, developmental profile could be used to estimate cognitive functioning of preschooler children with ASD. Therefore, even if cross-sectional studies can be extremely useful for generating hypotheses, these hypotheses need to be further confirmed by longitudinal investigation.

Thus, the aim was to evaluate the longitudinal cognitive profile from the first evaluation to IQ assessment, addressing three questions: 1) At each time point, does the ASD group show a different developmental profile compare to

typically-developing? 2) Is there one or more PEP domains at the first time point related to final IQ level? 3) What is the prevalence of ID in our ASD sample?

61 ASD and 18 Typically-Developing (TD) matched children were assessed at 3 time points, each 12-24 months apart (mean age at Time 1: ASD=3.4±0.2 years; TD=4.1±0.4 years). ASD subjects were diagnosed using ADI-R and ADOS-G. No differences were detected on treatment strategies among ASD. PEP-3 (T_1 and T_2) and Leiter-R (T_3) were administered to all participants.

At T_1: All PEP-3 domains exhibited a greater developmental delay in ASD compared to TD, also distinguished for typical disharmonic profile that showed expressive language, visual-motor imitation and social reciprocity as areas of weakness. At T_2: On gross motor, visual-motor imitation and affective expression subtests no significant differences were observed between ASD and TD.

All PEP-3 domains at T_1 not revealed significant correlation with Leiter-R IQ at T_3.

In our sample of ASD, the prevalence of ID was 29% (mean IQ=88.9±15.7).

In conclusion, although, at baseline our data confirm a greater developmental delay (also on cognitive domain) in all ASD children, only the 29% of these subsequently shows an intellectual disability. Moreover, no correlation between PEP-3 scores and IQ levels was detected; thus, a developmental delay should not be used to predict lower IQ level.

Finally, a better understanding of the cognitive level may not only have positive implications for an early diagnosis but also for intervention and long-term outcome, as well as to differentiate cognitive phenotypes in the clinical research.

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Chapter 1: Autism Spectrum Disorders

Children, adolescents and adults who have a diagnosis of autism spectrum disorders (ASDs) show their core symptoms on three domains: social functioning, reciprocal communication and peculiar patterns of behavior and interests.

Indeed, the term "autism spectrum disorders" refers to a class of neurodevelopmental disorders characterized by qualitative impairments in the development of social and communication skills, often accompanied by stereotyped and restricted patterns of interests and behavior, with onset of impairment before 3 years of age, throughout the life span. (APA, 2000).

To date, ASDs include the diagnostic categories of autism, pervasive developmental disorder not otherwise specified, and Asperger's syndrome.

1.1 A brief history

Autism does not have a long history, and this is due to the fact that the history of autism really didn't begin until the first decade of the 20th century. Although, autism as a condition was around prior to this time, it was not a recognized condition and most people would have been regarded as insane.
Indeed, the history of autistic disorders stretches far back into the mists of time, long before Kenner´s and Asperger´s insights (Brauner and Brauner, 1986). Some versions of the myths of changeling children, left in place of real human babies who had been stolen by fairies, are remarkably like children with autism.

Beyond the myths and legends, the word "autism", which has been in use for about 100 years, comes from the greek word "autos" meaning "self". The term describes conditions in which a person is removed from social interaction; hence, an isolated self. Eugen Bleuler, a Swiss psychiatrist, was the first person to use the term. He started using it around 1911 to refer to one group of symptoms of schizophrenia (Bleuler, 1911). To begin with, there was the unfortunate choice of name, which immediately led to confusion with Bleuler's use of the same term to refer to the active withdrawal into fanatsy shown by schizophrenic patients. Although Bleuler may have been the first to recognize one of the most common traits of autistics, there were three other pioneers of autism who really set the wheels of autism research in motion.

In the 1940s, researchers in the United States began to use the term "autism" to describe children with emotional or social problems. Leo Kanner, a doctor from Johns Hopkins University, used it to describe the withdrawn behavior

of several children he studied. At about the same time, Hans Asperger, a scientist in Germany, identified a similar condition that's now called Asperger's syndrome. Autism and schizophrenia remained linked in many researchers' minds until the 1960s. It was only then that medical professionals began to have a separate understanding of autism in children.

Leo Kanner was an Austrian-American psychiatrist, who was one of the first to specialize in child psychology. Kanner, a doctor at Baltimore's Johns Hopkins Hospital, is credited with recognizing autism as its own unique mental disorder. According to the history of autism, Kanner created the label early infantile autism, which he wrote about in 1943 in the journal "The Nervous Child". In his report (Kanner, 1943), Kanner discussed his research based on a group of eleven children who all closely displayed the following traits: social interaction difficulties, difficulty processing and adapting to changes, particularly good memory, echolalia , exceedingly sensitive to sounds, food issues and good intellectual potential.

Hans Asperger, was a scientist and pediatrician. He's best known in the history of autism for defining Asperger Syndrome. He studied 4 young boys and, like Kanner, found that each child displayed similar characteristics. He identified these characteristic behaviors as autistic psychopathy (Asperger, 1944). Although Asperger identified most of the same traits as Kanner, he didn't note his group having delayed echolalia. Alternatively, he said that the children had clumsy movements and irregular motor skills compared to regular children, and also that they talked much like grown ups. Asperger referred to them as "little professors". Unfortunately, the findings of Dr. Hans Asperger regarding autism were not

widely discovered until the late 1980′s even though his reports occurred much earlier in the history of autism. It is believed that there were two main reasons why Asperger did not receive the recognition he deserved until much later than his original observations. The first reason was his findings were delayed due to World War II. The second was that his work wasn't written in English and was not translated until almost 50 years later.

Bruno Bettelheim was an Austrian-American writer and child psychologist. He developed his own theories on autism and is best known for his theory of the "refrigerator mother". In his work "The Empty Fortress" (Bettelheim, 1967), wrote about three therapy sessions with children who had infantile autism. He claimed that their disorder was caused by having emotionally cold mothers. His theory was widely accepted, and for many years, parents (particularly mothers) were considered the problem behind autism.

Nevertheless today, Bettelhiem's theory has been disregarded by most, these three doctors had a huge impact on what people believed autism was in the mid 1900′s, as well as how the disorder is recognized today.

1.2 The changing epidemiology

The rate of pervasive developmental disorders is higher than reported 15 years ago (Fombonne, 2009).

Indeed, in the last 15 years, epidemiological surveys of pervasive developmental disorders have shown increasing prevalence estimates that reflect a broadening of the concept and diagnostic criteria for autism as well as increased awareness and improved detection of pervasive developmental disorders at all ages and all levels of intellectual ability (Fombonne, 2003; Bertrand et al., 2001; Scott et al., 2002).

Chakrabarti and Fombonne (2005) showed that the correlation between prevalence and year of publication was statistically significant and studies with prevalence more than 7/10,000 were all published since 1987. These findings point toward an increase in prevalence estimates in the last 15–20 years. Moreover, in their research found a prevalence for all pervasive developmental disorders near 60 per 10,000. Pervasive developmental disorder not otherwise specified is the most frequent subtype, and it occurres at about 1.7 times the rate of autistic disorder in the combined samples from the two surveys and Asperger's syndrome is less frequent than the two other subtypes.

Recently, epidemiologic surveys of autism and PDDs have now been carried out in several countries. Methodological differences in case definition and case finding procedures make between survey comparisons difficult to perform. However, from recent studies, a best estimate of 60 to 70/10,000 (6 to 7/1,000; or 0.6 to 0.7%; or one child in about 150 children) can be confidently derived for the prevalence of autism spectrum disorders (Fombonne, 2009).

The meaning of the increase in prevalence in recent decades could be ralated with the evidence that the broadening of the concept, the expansion of diagnostic criteria, the development of services, and improved awareness of the condition have played a major role in explaining this increase, although it cannot be ruled out that other factors might have also contributed to that trend (Lord, 2011).

Finally, it should be remembered that the concept of pervasive developmental disorders and of a spectrum of autistic disorders is relatively new. Previous epidemiological investigations mostly concentrated on autistic disorder, often on a much narrower definition of autistic disorder than that currently employed. In prior surveys, a relatively high number of children described with different labels (Fombonne, 2003) did not meet the full criteria for autism and were usually not incorporated in prevalence calculations. However, one of the few studies conducted more than 30 years ago that yielded useful information for such a comparison is that by Wing and Gould (1979), who identified a group of children encompassing more than just those with classical autism and referred to as exhibiting a triad of impairments. The prevalence of this broader disorder was 20 per 10.000, and if we take the data from that study as a baseline, recent prevalence figures point therefore toward a threefold increase in the prevalence of pervasive developmental disorders (Fombonne, 2003).

1.3 Clinical features

Any account of the definition of the clinical features of autism should be start with Kanner's careful and systematic observations on the eleven child with a previously unrecognized syndrome. These features include inability to develop relationship, a delay in speech acquisition, the non-communicative use of speech after it developed, echolalia, pronominal reversal, repetitive and stereotyped play activities, an obsessive insistence on the maintenance of sameness, a lack of imagination, a good rote memory and a normal physiacl appearance.

There was no doubt that autistic children existed, but equally there was considerable confusion over the boudaries of the syndrome (Rutter, 1974).

A differentiation had to be made between behaviors that could occur in autism (but that also occurred in other conditions) and those behaviors that were specially characteristic of autism. In doing this it was obviously important to control for age, sex, IQ, and presence of psychiatric disorder in order to ensure that any differences found were not merely a reflection of the fact that children's behavior varies according to these non-specific features. When this was done, it was found that three broad groups of symptoms were found in almost all children diagnosed as suffering from autism.

Core symptoms

Impaired Social Relationships. Several studies have shown that autistic children's social development has a number of rather distinctive features. First, there is a lack of attachment behavior and a relative failure of bonding that is most

marked in the first 5 years. Unlike normal toddlers, autistic children tend not to follow their parents about the house and they do not run to greet them when the parents return after having been out. They tend not to go to their parents for comfort when they are hurt or upset, and almost always they do not develop the bedtime kiss and cuddle routine followed by so many normal children. However, they do not usually physically withdraw from people and may enjoy a tickle or a rough-and-tumble. In the 1st year, quite often they do not take up an anticipatory posture or put up their arms to be picked up in a way taht normal children do.

On the other hand, especially in the more intelligent autistic children, social abnormalities may not be obvious until well into the 2nd year of life.

Lack of eye-to-eye gaze is usually said to be characteristic of autistic children. However, clinical observation suggests taht it is not so much the amount of eye-to-eye gaze but rather the way eye-to-eye gaze is used that is characteristic. Indeed, autistic child does not use eye-to-eye gaze in a highly discriminating fashion, looking up at people's faces when he wants to gain their attention, when he wants to be picked up, when he is being aggressive toward them, or when he is being spoken to.

After age 5 years, many of the social impairments may no longer be evident (at least, not to the same degree), but serious social difficulties continue. This is most evident in a lack of cooperative group play with other children, a failure to make personal friendships, and a lack of empathy and a failure to perceive other people's feelings and responses.

Language and pre-langauge skills. Not only are autistic children usually markedly delayed in their acquisition of speech, but also their pattern of language

development and their use of language is strongly different from those of children with normal devolpment or with other language disorders. First of all, there are serious impairments in a variety of skills that are often thought to underlie or precede language. Autistic children usually fail to show much social imitation. They do not wave “bye-bye”, they do not participate in imitative games, and they are less likely to copy or follow their parents’ activities. They are delayed in their meaningful use of objects so that when they are very young they may spin the wheels of a toy car or put the car in their mouth rather than use it in the intended way. They are unlikely to engage in pretend games, such as mothers and fathers, schools, or cowboys and indians. Sometimes an autistic child does have some make believe actions in which he engages, but if so, these tend to be stereotyped and repetitive.

Almost they tend to make their needs known by taking the adult by the wrist, often they do not point and rarely is it accompanied by mime, demonstration, or symbolic gesture.

However, in those who do learn to speak there are a variety of characteristic abnormalities. First, immediate echolalia and the delayed repetition of stereotyped phrases is usual for quite a long period after speech first develops. Characteristically, this is accompanied by I-You pronominal reversal. Secondly, speech tends not to be used in the usual way for social communication. Thus the autistic child tends to talk much less than the normal child of a comparable level of language development. What they say is less often related to what they have heard and they give the impression of talking to someone rather than with someone.

Also, they are usually very poor in talking about anything outside the immediate situation so that they do not, for example, tell their parents what they have done at school during the day. However, often the autistic child's use of words is somewhat unusual, with curious metaphors and odd ways of putting things.

Insistence on Sameness. The term insistence on sameness is not a very satisfactory one, in that it involves inferences. However, since Kanner's original description it has been widely used to cover a variety of stereotyped behaviors and routines. Characteristically, in early childhood, there are rigid and limited play patterns that lack both variety and imagination. For one thing, the children may endlessly line up toys, make patterns of house- hold implements, or collect curious objects such as tins or stones of a special shape. Second, there may be intense attachments to these objects, so that the children have to carry round with them a piece of grit in the fold between the thumb and the index finger, or they have to have a particular belt at all times. Usually these attachments persist in spite of extreme distor- tions in the size or shape of the object, so that the function of the object is irrelevant to the attachment. The attachment is to a specific object and the children protest if it is removed. However, if the object is not eventually returned to the child, attachment to a new object frequently takes place. Third, especially in middle childhood and later, many autistic children have unusual preoccupations that they fol

low to the exclusion of other activities. Typically these involve things like bus routes, train timetables, colors, numbers, and patterns. Sometimes, the preoccupation takes the form of repeatedly asking stereotyped questions to which specific answers must be given. Fourth, ritualistic and compulsive phenomena are very common. In early and middle childhood these usually take the form of rigid routines but in adolescence it is not infrequent for them to develop into frankly obsessional symptoms, with touching compulsions and the like. Fifth, there is sometimes a marked resistance to changes in the environment so that the child becomes extremely distressed if furniture in the house is moved or if the ornaments are changed.

Although ASDs are defined by the shared difficulties mentioned above, anyone who has met more than one person with an ASD is struck by the differences between these individuals.

The signs in young children

In the past 10 years several new sources of information on the characteristics of children with ASD in the first 2 years of life have become available. Adrien et al. (1993) found that within the first year children with autism showed impairments in social interaction, lack of social smile, lack of appropriate facial expression, hypotonia and poor attention. In the second year of life additional impairments included ignoring people, preference for aloneness, lack of eye contact, lack of appropriate gestures and lack of emotional expression. In a recent well-controlled study that addressed this issue, Baranek (1999) found that abnormalities in

orientation to visual stimuli, aversion to touch and delayed response to name all characterised autism (but not developmental delay or typical development) as early as 9 months of life. These findings, allied with other research focus on early pre-verbal social communication and social orientating behaviours. Behaviours such as responding to name and monitoring gaze are present in nearly all typically developing infants by the end of the first year of life. Further, they are associated with word learning, later language and theory of mind development. They are early emerging signs of social interest and social orientation to familiar adults and their absence in the second year of life is highly indicative of autism (Charman and Baird, 2002). There is also some evidence of early abnormalities in sensory, motor, repetitive and stereotyped behaviours from these retrospective video studies, and when such behaviours are present they are highly characteristic of autism. However, most studies concur that the best discriminators at this age are likely to be the social and communicative impairments. Infants with ASD produced few examples of spontaneous pretend play; however, two-thirds of them produced some examples of functional play. Both cross-sectional and longitudinal studies support the view that the nature of the ASD-specific impairments changes with age and developmental level.

Summarizing, in early childhood subjects who are later diagnosed with autism may be distinguished from low-risk controls on the basis of: (1) several specific behavioral markers, including atypicalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect, and sensory-oriented behaviors; (2) prolonged latency to disengage visual attention; (3) a characteristic pattern of early

temperament, with marked passivity and decreased activity level at 6 months, followed by extreme distress reactions, a tendency to fixate on particular objects in the environment, and decreased expression of positive affect by 12 months; and (4) delayed expressive and receptive language (Zwaigenbaum et al., 2005).

In the context for early diagnosis several factors have contributed to the decrease inthe age of referral and diagnosis of autism. Firstly, there has been an increase in recognition of the early features of autism amongst primary healthcare practitioners and this has led to earlier referral to paediatric and child development specialists (Baird et al., 2001). There has been more media and public interest in the topic, with publication of personal stories and descriptions of children's behaviour, which guide parents to instigate referral. Secondly, attempts have been made to prospectively identify cases of autism using screening instruments. Thirdly, there is increasing evidence that appropriately targeted intervention improves outcome in children with ASD. Another impetus for the promotion of earlier identification is the fact that the risk of having a subsequent child with autism following an earlier child with autism is 5%, many times even the highest reported prevalence rate. Parents need to have information about diagnosis as soon as possible if they are to make informed choices about extending their family (Simonoff, 1999), although little is known as yet of the effect of genetic advice and information in autism.

1.4 Intellectual functioning

Originally, Kanner (1943) had thoght that autistic children were really of normal intelligence and that their poor functioning was simply a secondary consequence of their autistic failure to make relationships children's often good rote memory, their serious facial expression, and lack of physical signs were in keeping with this view, which many other past writers. It was important to test this hypothesis by further examination of the nature of intellectual performance in autistic children. However, ASD was once considered to be highly associated with intellectual disability and to show a characteristic IQ profile; with strengths in Performance over Verbal abilities and a distinctive pattern of 'peaks' and 'troughs' at the subtest level. However, there is little data from epidemiological studies.

The long-established view of intellectual abilities in autism spectrum disorders (ASD) was that up to 75% of individuals had an intellectual disability (previously referred to as 'mental retardation'; Schalock et al., 2007); defined by an IQ<70, alongside accompanying impairment in everyday functioning. Furthermore, a widespread clinical view is that Performance IQ (PIQ) was commonly higher than Verbal IQ (VIQ) (Mayes & Calhoun, 2003). Another widely accepted view is that at a subtest level (e.g., on Wechsler intelligence tests) a characteristic profile of strengths (or 'peaks') on subtests such as Block Design and weaknesses (or 'troughs') on subtests such as Comprehension is found (Happé, 1995).

However, many of these widely held views about the intelligence of

children with an ASD were first formed several decades ago when our conceptualisation of autism, in terms of to whom the diagnosis is applied and how prevalent the disorder is, was very different from today and historical data might not apply to children who currently receive an ASD diagnosis (Fombonne, 2009). Most studies have used clinically ascertained cohorts and there has been limited evidence presented within an epidemiological framework. The prevalence of ASD is now recognised to be between 60 and 116 per 10,000, depending on the strictness with which the diagnostic criteria are applied (Chakrabarti & Fombonne, 2005).

There is evidence from recent epidemiological studies that only approximately 50% of children with ASD have intellectual disability (IQ <70) (Bertrand et al., 2001; Chakrabarti & Fombonne, 2005), although this rose to approximately 60% and 70%, respectively, for the more narrowly defined autism group. However, both these studies had only moderate sample sizes (N=42 Bertrand et al., 2001; N=57 with cognitive data Chakrabarti & Fombonne, 2005).

Recents data from the SNAP project (Charman et al., 2011) show that the 55% of children with ASD had an intellectual disability (IQ<70) but only 16% had moderate to severe intellectual disability (IQ<50). 28% of children with ASD had average intelligence (115>IQ>85) but only a minority (3%) were of above average intelligence (IQ>115). There was some evidence for a clinically significant PIQ/VIQ discrepancy but discrepant verbal versus performance skills were not associated with a particular pattern of symptoms, as has been previously reported. There was mixed evidence of a characteristic subtest profile: Whilst some previously reported patterns were supported (e.g. poor Comprehension);

others were not (e.g. no ‘peak’ in Block Design). Adaptive skills were significantly lower than IQ and were associated with severity of early social impairment as well as IQ.

Thus, in recent epidemiological studies, ASD is less strongly associated with intellectual disability than traditionally held and there is only limited evidence of a distinctive IQ profile. However, adaptive outcome also remain significantly impaired even for those children of average intelligence.

1.5 Available knowledge on causes

Genetic factors

Greater public awareness of autism has led to increased funding for autism research, yet the cause of ASD remains largely unknown because of the complex behavioral phenotypes and multigenic etiology of this disorder. The highly variable cognitive manifestations of the ASDs range from a nonverbal child with severe mental retardation and self-injury to a high-functioning college student with an above-average IQ despite impaired language use and inadequate social skills. Mental retardation thus is not a defining criterion for autism (albeit certain cognitive abilities are characteristically affected), but the mean distribution of IQs is lower than average, and the likelihood of retardation increases with more widespread brain dysfunction. Like mental retardation, autism is a behaviorally defined syndrome with a wide variety of both genetic and nongenetic causes. With the exception of Rett syndrome, which is caused in the majority of cases by de novo mutations or microdeletions of the methyl-CpG-binding protein 2 (MeCP2) gene on Xq28,13 there is no current evidence that the other DSM-IV subtypes of autism are linked to any particular genetic or nongenetic disorder.

Current evidence indicates that multiple genetic factors are the causative determinants of the majority of cases of autism (rutter et al., 1994).

Autism is frequent in tuberous sclerosis complex and fragile X syndrome, but these 2 disorders account for but a small minority of cases. Currently, diagnosable medical conditions, cytogenetic abnormalities, and single-gene defects (eg, tuberous sclerosis complex, fragile X syndrome, and other rare diseases) together

account for <10% of cases. There is convincing evidence that “idiopathic” autism is a heritable disorder. Epidemiologic studies report an ASD prevalence of ~3 to 6/1000, with a male to female ratio of 3:1. This skewed ratio remains unexplained: despite the contribution of a few well characterized X-linked disorders, male-to-male transmission in a number of families rules out X-linkage as the prevailing mode of inheritance. The recurrence rate in siblings of affected children is ~2% to 8%, much higher than the prevalence rate in the general population but much lower than in single-gene diseases. Twin studies reported 60% concordance for classic autism in monozygotic (MZ) twins versus 0 in dizygotic (DZ) twins, the higher MZ concordance attesting to genetic inheritance as the predominant causative agent. Reevaluation for a broader autistic phenotype that included communication and social disorders increased concordance remarkably from 60% to 92% in MZ twins and from 0% to 10% in DZ pairs. This suggests that interactions between multiple genes cause “idiopathic” autism but that epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits. The identity and number of genes involved remain unknown. The wide phenotypic variability of the ASDs likely reflects the interaction of multiple genes within an individual's genome and the existence of distinct genes and gene combinations among those affected. There are 3 main approaches to identifying genetic loci, chromosomal regions likely to contain relevant genes: 1) whole genome screens, searching for linkage of autism to shared genetic markers in populations of multiplex families (families with >1 affected family member); 2) cytogenetic studies that may guide molecular studies by pointing to relevant inherited or de novo chromosomal abnormalities in

affected individuals and their families; and 3) evaluation of candidate genes known to affect brain development in these significantly linked regions or, alternatively, linkage of candidate genes selected a priori because of their presumptive contribution to the pathogenesis of autism (Muhle et al., 2004). Data from whole-genome screens in multiplex families suggest interactions of at least 10 genes in the causation of autism. Thus far, a putative speech and language region at 7q31-q33 seems most strongly linked to autism, with linkages to multiple other loci under investigation. Cytogenetic abnormalities at the 15q11-q13 locus are fairly frequent in people with autism, and a "chromosome 15 phenotype" was described in individuals with chromosome 15 duplications. Among other candidate genes are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22-q33 and the $GABA_A$ receptor subunit and UBE3A genes on chromosome 15q11-q13. Variant alleles of the serotonin transporter gene (5-HTT) on 17q11-q12 are more frequent in individuals with autism than in nonautistic populations. In addition, animal models and linkage data from genome screens implicate the oxytocin receptor at 3p25-p26. Most pediatricians will have 1 or more children with this disorder in their practices. They must diagnose ASD expeditiously because early intervention increases its effectiveness. Children with dysmorphic features, congenital anomalies, mental retardation, or family members with developmental disorders are those most likely to benefit from extensive medical testing and genetic consultation. The yield of testing is much less in high-functioning children with a normal appearance and IQ and moderate social and language impairments. Genetic counseling justifies testing, but until autism genes are identified and their functions are understood, prenatal diagnosis will exist only

for the rare cases ascribable to single-gene defects or overt chromosomal abnormalities. Parents who wish to have more children must be told of their increased statistical risk. It is crucial for pediatricians to try to involve families with multiple affected members in formal research projects, as family studies are key to unraveling the causes and pathogenesis of autism. Parents need to understand that they and their affected children are the only available sources for identifying and studying the elusive genes responsible for autism. Future clinically useful insights and potential medications depend on identifying these genes and elucidating the influences of their products on brain development and physiology.

Neurobiological basis

If the brain is responsible for behavior then it should follow that disordered autistic behaviors should be explainable in terms of brain abnormalities and disordered neurobiological processes. While findings are generally speculative and the etiology of the disorder remains somewhat of an enigma, there is significant evidence that autism is associated with neurobiological dysfunction.

There is evidence that autism is associated with specific structural brain abnormalities. Relatively recent research in this area has been conducted by Courchesne et al. (1994), in conjunction with the San Diego Children's Hospital and the University of California in San Diego. Using magnetic resonance imaging (MRI) to contrast the brains of normal subjects with those of individuals with autism, Courchesne has found that certain areas of the cerebellum are distinctly

underdeveloped in autistics. The cerebellum is a relatively large portion of the brain located near the brain stem that is primarily responsible for motor movements, but may also play a role in speech, learning, emotions, and attention. Thus, cerebellar abnormalities may help to explain the aberrant motor activity, impaired cognitive abilities, and apparent lack of emotion that are characteristic of autism. In particular, results of comparative brain imaging studies have shown that two areas of the cerebellum, vermal lobules VI and VII, are significantly smaller in autistic individuals. These regions of the cerebellum are connected to brain regions that specifically govern attention, arousal, and the assimilation of sensory stimulation. Based on such results, Courchesne has developed a "Theory of Overstimulation" that emphasizes the idea that autistic individuals are chronically overstimulation by confusing and inconsistent activity of their disordered brains. He suggests that individuals with autism are abnormally subject to stimulation because of specific brain deficiencies and that, as a result, they try to shield themselves from additional stimuli. Courchesne takes the theory one step further to suggest that there is a brain mechanism through which repetitive and rhythmical behavior can have a calming effect on the cerebral cortex. Thus, certain characteristic features of autism, including sensitivity to sensory stimuli and repetitive behavior, may be explained in terms of structural abnormalities in the cerebellum. There is also evidence that autistic individuals have dramatically reduced levels of Purkinje cells in the cerebellum. These cells, which are rich in the neurotransmitter serotonin, transmit inhibiting messages from the cerebellum to areas of the cerebral cortex. Given that the cerebral cortex is thought to be the

center of thinking and judging, the dearth of communication with this area may help to explain some of the cognitive deficits characteristic of autism.

Evidence has also suggested that autism may be related to specific neurological damage to the limbic system. Bauman and Kemper (1985) have examined post-mortum brains of autistic individuals and have found the amygdala and the hippocampus to be underdeveloped. In particular, they have reported finding densely packed, unusually small neurons in the amygdala and hippocampus of autistic individuals. While the exact implications of these findings remain somewhat speculative, examination of the normal functions of these structures as well as related animal research may help to explain how such neurological damage may be connected to the traits and behaviors associated with autism.

The amygdala is thought to play a role in the control of aggression and emotion. This is significant in that autistics are often either overly aggressive or passive and may appear emotionless. When the amygdala is damaged or removed, animals exhibit social withdrawal, compulsive behaviors, failure to learn about dangerous situations, memory deficits, and difficulty adjusting to novel situations characteristics that are similar to those seen in autism. The amygdala may also function in response to various types of sensory stimuli, another system which appears to function abnormally in autistics (Critchley et al., 2000).

The hippocampus is thought to be primarily responsible for learning and memory. It has been hypothesized that autistic individuals have a specific cognitive deficit related to learning and memory. When the hippocampus is damaged or removed, animals demonstrate an inability to store new information

into memory and they often display characteristics commonly seen in autism, including stereotypic, self-stimulatory behaviors, and hyperactivity (Schumann et al., 2004).

Several findings have implicated neurochemical dysfunctions in individuals with autism. Additionally, there is some evidence that therapeutic medications which act directly on these neurochemical systems (including fenfluramine, haloperidol, risperidone, clonidine, and naltrexone) can effectively decrease the aggressive, obsessive-compulsive, and self-stimulating behaviors associated with autism in controlled drug trials.

Indeed, autism has been associated with abnormalities of the brain domaminergic system. Specifically, it is thought that autistic individuals have increased levels of brain dopamine. This is demonstrated by the fact that intellectually subnormal autistic children with severe hyperactivity and stereotypes have been shown to have high cerebrospinal fluid levels of levels of the dopamine metabolite homovanillic acid. Furthermore, the use of dopamine antagonists such as haloperidol has been shown to have modest success in decreasing hyperactivity, negativism, and stereotyped behaviors, and facilitating learning in autistics. The dopaminergic system is known to affect motor behavior. Abnormalities of this system are associated with excess motor activity and stereotyped behaviors, traits often observed in autistic patients. It has also been hypothesized that autism is related to a dysfunctional serotonergic system, and that such dysfunction may be responsible for the sensory and perceptual abnormalities seen in these patients. Evidence for this theory comes in part from studies that have shown increased platelet serotonin concentrations in autistic individuals. Additionally, studies of

fenfluramine, a medication that reduces brain serotonin, have shown that the drug may be beneficial in treating some cases of autism. There is also evidence that some autistic individuals have elevated levels of beta-endorphins, an endogenous opiate-like substance in the body. It has been shown that neonatal rats and chicks exposed to high levels of opiates show autistic-like symptoms after they are born. In addition, opiate addicts often demonstrate social withdrawal, self-stimulation, and high levels of pain tolerance - symptoms often associated with autism. While such evidence suggests that opiate antagonists such as naltrexone may be beneficial in treating autism, such a treatment has not proven to be very effective. Abnormalities of the noradrenergic system have also been associated with autism. In particular, norepinephrine agonists have been shown to worsen the behaviors of autistic patients, and increases in norepinephrine plasma concentrations have been reported in autistics.

Thus, it seems that there are several structural and neurochemical abnormalities associated with autism that can help to explain the specific behaviors and deficits characteristic of the disorder. This demonstrated link between brain and behavior is significant on several levels. In terms of the etiology of the specific disorder, localization of physiological dysfunction suggests biological, rather than psychological, social or otherwise non-biological causality.

Psychological theories

Following the error of the early ‘‘blame the parent’’ notion, speculation about how autism might be understood through psychology was held back in some

important ways. Over the last two decades, new theoretical models have been proposed that try to understand the developmental and behavioral aspects of autism from the point of view of psychological development; it must be emphasized that this is an attempt to understand brain-based difficulties and not toblame the parents. These attempts are of some interest in terms of research and may, perhaps, lead to some treatment advances. It is important to realize that several rather different approaches have been used. One attempts to view the social problems in autism as one of many different difficulties caused by the same factor (or factors). The other view emphasizes the social difficulties as primary in some basic way, that is, as leading to other problems. These all have their pros and cons and none has, at least as yet, emerged as the ''winner.'' At present, they all have something to offer in terms of alternative models of how we might understand autism. The Theory of Mind approach has emphasized the idea that there is a basic problem for children with autism in empathizing with others, that is, having a ''theory of mind,'' or theory of what motivations, intention, and so on, impact on the behavior of others. This approach, first proposed by Baron-Cohen (1989) has been remarkably productive in terms of research. The simplicity and elegance of this theory have added to its attractiveness. There are, however, two problems with this model. One is that the severe difficulties in social interaction impact behaviors seen in very, very young children—children of a few weeks of age. This is a time well before the ability to ''put yourself into the other's place'' has really developed. Another problem is that many higher functioning individuals on the autism spectrum can do ''theory of mind'' tasks just fine, and yet these individuals are still very socially disabled.

Another approach, termed the executive dysfunction hypothesis, emphasizes deficits in ‘‘executive functions’’ (Ozonoff, 1991). The notion of executive functions refers, basically, to the whole range of abilities involved in planning and organization. For example, seeing the multiple steps involved in a complicated task, plotting a solution in terms of getting to the desired result, keeping the desired result in mind, and being able to work out alternatives when this is needed. Within this view, autism is related to difficulties in dealing with change and a tendency to engage in repetitive behavior and perseveration as well as to problems in developing planning and problem-solving abilities due to a lack of coordinated reasoning and ongoing adjustment to feedback. As we discuss later in this book, there is no question that children with autism spectrum disorders often have severe problems in this area. From the point of view of a more general theory, however, there are some difficulties. Probably most importantly, difficulties in this area are not unique and specific to autism; that is, children with attention deficit hyperactivity disorder also have problems with organization (but don’t have social troubles of the same type seen in autism).

A somewhat different theory proposes that the difficulties in autism relate to ‘‘weak central coherence’’ (Frith, 1989). The idea here is that people with autism have trouble getting the ‘‘big picture’’ issue; they don’t see the interconnections of things a ‘‘not seeing the forest for the trees’’ problem. This theory would account for some of the people with autism who are gifted in one area but very deficient in another area. Although very attractive in many ways, the experimental evidence has been somewhat weak and contradictory.

The "Fractionable Autism Triad"

Recently, Happè and Ronald (2008) hypothesized, despite half a century's research into ASD, that there is little evidence regarding the unity of the three core areas of impairment. Indeed, an early epidemiological study, which set in place the notion of the triad of impairments, remains the only full examination of this issue; these authors found some evidence of clustering of the three impairments. The key importance of this issue is that researchers have, for the last half century and with only a few notable exceptions (Goodman, 1989) been searching for the causes and cures for autism as a whole. Research on ASD at the behavioral, cognitive and genetic levels has proceeded on the assumption that the three impairments that define autism must be explained together. In this article, we question this basic assumption and present evidence at each of these levels that suggests the triad of impairments can be fractionated and should be studied separately. Behavioral features of autism: integral or fractionable? One of the challenges in establishing whether the triad of ASD features requires a unitary explanation or is, instead, fractionable, lies in the circularity of examining diagnosed populations. Because the diagnosis of autism (and even Asperger syndrome) requires impairments in each of the three key areas, examination of diagnosed populations cannot establish the potential fractionation of the triad. One way through this impasse is to explore the relationship between social, communicative and rigid/repetitive traits in the general population. Recent work suggests that whether a child joins in playing games with other children easily, can keep a two-way conversation going or likes to do things over and over again in the same way all the time. The distribution of such traits supports a smooth

continuum (at least at the behavioral level) between individuals meeting diagnostic criteria for ASD and individuals in the general population. Importantly, there is no evidence of a bimodal distribution, or 'hump' at the extreme, separating clinical from nonclinical levels of difficulty. In light of current research, the authors suggest that it is time to give up on the search for a monolithic cause or explanation for the three core aspects of autism, at the genetic, neural and cognitive levels. Clearly a question remains of why these three features co-occur at above-chance rates. At the genetic level, although the majority of genes appear to be symptom specific, there is evidence for a minority of overlapping genes between domains. At the cognitive level, impairments in more than one domain may interact; compensatory strategies may be reduced in the face of multiple impairments. Given the widespread comorbidity generally found in developmental psychopathology, what is most remarkable is the extent of fractionation among the three core aspects of autism.

The implications of the "traid autism fractionable" are as follows. First, behaviorally it would seem useful to measure the three aspects of the triad separately, rather than rely on global ratings of autism severity, or ratings that focus exclusively on social functioning. Secondly, molecular genetic studies, which have resulted in little by way of replicated linkage, should abandon the search for genes 'for autism' as a whole. Instead, we suggest approaches that will allow identification of genes contributing specifically to social, communicative or rigid/repetitive traits, as we believe that the majority of genes relevant to ASD will have symptom-specific action. Indeed, recent studies that have focused on subgroups within ASD, such as those showing high levels of insistence on

sameness or those with delayed onset of phrase speech, have shown stronger linkage signals. Heterogeneity within the autism spectrum is perhaps the biggest single obstacle to research at all levels. A third implication is that heterogeneity in ASD, on our account, is not simply due to noise or the complex unfolding of development, but is an unavoidable consequence of variation along at least three largely independent (although of course interacting) dimensions of impairment. Fourth, our argument and our findings within a large twin sample suggest that there may be many individuals with isolated impairments in one aspect of the triad, who do not meet diagnostic criteria for any recognized disorder, but show difficulties of comparable severity to those with autism. How we identify and meet the needs of these children and adults is a key challenge for the future.

Lastly, if different features of autism are caused by different genes, associated with different brain regions and related to different core cognitive impairments, it seems likely they will respond to different types of treatment.

Thus, abandoning the search for a single cause for a single entity of autism may also mean abandoning the search for a single 'cure' or intervention.

1.6 Diagnostic systems and instruments

The current approach to the diagnosis of autism, as exemplified in DSM-IV (APA, 1994) and ICD-10 (WHO, 1994), has worked reasonably well in terms of facilitating both research and clinical service. These gains have been reflected in the dramatic increase in research on autism and related conditions and an increased awareness on the part of the public and media (Fombonne, 2005). As expected, this increase in research has also raised important questions about syndrome boundaries in this heterogeneous group of conditions.

This includes the conditions currently 'officially' recognized (Asperger's disorder, Rett's disorder, Childhood distintegrative disorder) and the 'subthreshold' category either termed (in DSM-IV) Pervasive Developmental Disorder Not Otherwise specified (PDD-NOS) or (in ICD-10) atypical autism. Much less research has been conducted on the 'broader spectrum', although there has been much speculation about whether subgroups/subtypes exist and how they might best be conceptualized. Other tensions surround the issue of diagnosis as a 'ticket' for services – a problem referred to as diagnostic substitution (Fombonne, 2005). It is also commonly, but incorrectly, assumed that approaches to subtyping should be universally applicable, e.g., that classification for educational services eligibility must be the same as for etiological research. The ICD-10 addressed this issue, in part, by creating 'clinical' and 'research' criteria separately, while the DSM system utilizes one set of criteria for both uses.

Attending the DSM-V, these are to date the proposed criteria and rationale revisions:

- *Proposed criteria DSM-V on January 26, 2011*

(http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=94#)

[Autism Spectrum Disorder

Must meet criteria A, B, C, and D:

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction,

2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated- verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people

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

1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases).

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).

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

4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

D. Symptoms together limit and impair everyday functioning.]

- *Revisions rationale:*

(http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=94#)

[New name for category, autism spectrum disorder, which includes autistic disorder (autism), Asperger's disorder,childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified.

- Differentiation of autism spectrum disorder from typical development and other "nonspectrum" disorders is done reliably and with validity; while distinctions among disorders have been found to be inconsistent over time,

variable across sites and often associated with severity, language level or intelligence rather than features of the disorder.

- Because autism is defined by a common set of behaviors, it is best represented as a single diagnostic category that is adapted to the individual's clinical presentation by inclusion of clinical specifiers (e.g., severity, verbal abilities and others) and associated features (e.g., known genetic disorders, epilepsy, intellectual disability and others.) A single spectrum disorder is a better reflection of the state of knowledge about pathology and clinical presentation; previously, the criteria were equivalent to trying to "cleave meatloaf at the joints".

Three domains become two:

1) Social/communication deficits
2) Fixated interests and repetitive behaviors
    - Deficits in communication and social behaviors are inseparable and more accurately considered as a single set of symptoms with contextual and environmental specificities
    - Delays in language are not unique nor universal in ASD and are more accurately considered as a factor that influences the clinical symptoms of ASD, rather than defining the ASD diagnosis
    - Requiring both criteria to be completely fulfilled improves specificity of diagnosis without impairing sensitivity
    - Providing examples for subdomains for a range of chronological ages and language levels increases sensitivity across severity levels from mild to more severe, while maintaining specificity with just two domains

- Decision based on literature review, expert consultations, and workgroup discussions; confirmed by the results of secondary analyses of data from CPEA and STAART, University of Michigan, Simons Simplex Collection databases

Several social/communication criteria were merged and streamlined to clarify diagnostic requirements.

- In DSM-IV, multiple criteria assess same symptom and therefore carry excessive weight in making diagnosis
- Merging social and communication domains requires new approach to criteria
- Secondary data analyses were conducted on social/communication symptoms to determine most sensitive and specific clusters of symptoms and criteria descriptions for a range of ages and language levels

Requiring two symptom manifestations for repetitive behavior and fixated interests improves specificity of the criterion without significant decrements in sensitivity. The necessity for multiple sources of information including skilled clinical observation and reports from parents/caregivers/teachers is highlighted by the need to meet a higher proportion of criteria.

The presence, via clinical observation and caregiver report, of a history of fixated interests, routines or rituals and repetitive behaviors considerably increases the stability of autism spectrum diagnoses over time and the differentiation between ASD and other disorders.

Reorganization of subdomains increases clarity and continues to provide adequate sensitivity while improving specificity through provision of examples from different age ranges and language levels.

Unusual sensory behaviors are explicitly included within a sudomain of stereotyped motor and verbal behaviors, expanding the specfication of different behaviors that can be coded within this domain, with examples particularly relevant for younger children

Autism spectrum disorder is a neurodevelopmental disorder and must be present from infancy or early childhood, but may not be detected until later because of minimal social demands and support from parents or caregivers in early years.]

A combination of instruments was developed for assessing ASD in children and adolescents: the Autism Diagnostic Interview-Revised (Lord et al., 1994) and the Autism Diagnostic Observation Schedule-Generic (Lord et al., 1989). Both instruments provide extensive data on the three aspects of ASD, as mentioned in DSM-IV and ICD-10: qualities of reciprocal social interaction; communication and language; and repetitive, restricted, and stereotyped interests and behaviors. When used together, data are available both on the current behavior (observation with ADOS-G) and on the history and development of the child (interview with parents/caregivers with ADI-R). The algorithm of the ADI-R differentiates between autistic and nonautistic, and the algorithm of the ADOS-G differentiates between autistic, PDD-NOS, and non-PDD.

1.7 Non-pharmacologic interventions

It is now widely acknowledged that, to date, the forms of treatment enjoying the broadest empirical validation for effectiveness with individuals with autism are those treatments based upon a behavioral model. These treatments all have as their foundation the systematic application of the psychological principles of learning to human behavior. This form of treatment is derived from the experimental analysis of behavior, which is a science dedicated to understanding the laws by which environmental events determine behavior. By understanding these laws, we can develop applications to change behavior. The science wherein these principles are applied to the improvement of socially important behaviors is known as applied behavior analysis, and the development of the behavioral treatment of autism is largely the result of this field of science.

The first demonstrations of the effectiveness of this treatment model were provided in the 1960s when highly structured operant learning programs were employed to improve the condition of children with autism (Lovaas et al., 1967). These early programs had a tremendous impact because they were the first to affect empirically validated gains in children with autism after no other form of treatment had been successful. These behavioral programs were successful in increasing language, social, play, and academic skills, as well as in reducing some of the severe behavioral problems often associated with the disorder. However, as effective as these early demonstrations proved to be, enthusiasm was somewhat tempered when generalization and follow-up data indicated some limitations to their effectiveness (Lovaas et al., 1973).

It is a testament to the behavioral model and its emphasis on careful data collection and analysis that specific areas requiring further research were

identified. Subsequent research has addressed these areas, allowing for improvement in the effectiveness of treatments based on this model. Along these lines, the field has evolved and broadened to include comprehensive behavioral packages and behavioral strategies that have more widespread and durable treatment outcomes (Schreibman, 2000). Many of these recent behavioral treatment extensions have been put to the empirical test (with varying degrees of experimental rigor).

Space constraints preclude describing the extensive literature in this area here in any detail, and it is not the purpose of this dissertation to present a comprehensive and inclusive discussion of the research in this area. Rather, it was the intent to make some general comments about the current state of behavioral treatments and where future research needs to be directed.

1.8 Pharmacotherapy

On the basis of the above literature review, some clinical with guidelines can be proposed. There is no pharmacotherapy of ASDs, but a pharmacotherapy of some symptoms is possible. Thus, pharmacotherapy should be considered only when the severity of symptoms hampers other psychosocial, rehabilitative and psychoeducational treatment programs.

Given the symptomatic nature of the pharmacologic intervention, it is not surprising that there is no consensus on the first choice medication in ASDs, the choice being determined by the target symptoms. However, a symptom-targeted approach may be misleading, inducing a polypharmacy or an excessively changing strategy, given that autistic children often present many maladaptive symptoms. A possible strategy is to define broad symptomatologic domains which can orient a first pharmacologic approach, and at same time to prefer medication with the broadest range of effects.

Acoording to the firts issue, four possible symptomatologic domains can be defined: impulsivity, aggresion against self and others; repetitive phenomena; mood swings, tempere tantrums; severe isolation with stereotypies.

According to the second issue, data from the literature suggest that a typical antipsychotics, SSRIs, and mood stabilizers present the broader spectrum of clinical effects.

According to both these criteria, when aggression or self-injurious behaviours are the target symptom, a trial with an atypical antipsychotic (risperidone) can be started at low doses (RUPP, 2011). When repetitive phenomena are prevalent, an SSRI (fluoxetine), can be considered (De Long at al., 2002). When mood swings

and temper tantrums are more evident, a mood stabilizer (valproic acid) can be the first choice (Hollander et al., 2001). The pharmacologic management of severe isolation with sterotypies is more complex, this symptomatologic domain being particularly resistant to any kind of interevtion, including medication. However, a trial with a low-dose atypical antypsychotic may reduce the severity of isolation and increase the effectiveness of co-administered non-pharmacologic treatments.

A careful psychiatric assessment may reveal possible comorbid conditions, often masked by the autistic symptomatology. These comorbidities (anxiety, depression, bipolar disorder, ADHD) may be the target of pharmacologic treatment, according to the guiding principles for each specific comorbid disorder. Severe sleep disorders may be managed using niaprazine, or mirtazapine or trazodone, especially when other anxiety disorders are comorbid. Benzodiazepines may determine a behavioral activation in younger patients.

When a combination of symptomatologic domains is present, only the must impaired domain should be considered with a monotherapy. Only when a trial with a single medication has been performed, with a partially positive but unsatisfying response, may an association with an other medication be carefully started, monitoring possible emerging side-effects. It is important to remember that fluvoxamine, more than other SSRIs, when added to an antipsychotic, can elevate the serum levels of the antipsychotic.

Unfortunately, treatment non-response is not rare. After unsatisfying trials according to the above mentioned principles, alternative options, less supported by empirical evidence, can be considered.

Methylphenidate (Di Martino et al., 2004) and clonidine/guanfacine in ADHD-like symptoms, propanolol in explosive behavior disorders, and naltrexone in self-injurious behavior can be used an alternative or adjunctive medication, when these symptoms did not improve after treatment with the previously reported medications. This is particularly true in the case of self-injurious behavior, an extremely treatment-resistant symptom in autistic and/or mentally retarded children, which always requires a multi-modal intervention, including behavioral techniques and parental support.

However, there is no consensus on the use of psychopharmacological treatments in autism; because, although there exist many clinical observations, only few controlled studies have validated the efficiency and safety of these treatments.

Chapter 2: A longitudianl study from developmental profile to IQ level in ASD

Autism spectrum disorders are developmental disabilities that appear before age three and occur throughout the entire lifespan, although it is not yet clearly known which is the natural course of the syndrome.

People with autism show differences in the development of their cognitive function, language, behavior and social skills, with impairment in their flexible imaginative funcutions and, both qualitative and quantitative, changeable presence of restricted and repetitive behaviors and interests.

These difference, though they involve serious difficulties in the global functioning of these subjects, may result in sometimes savant performance, such as calculation, musical abilities or photographic memory.

2.1 Background

Over the last decade or more, besides an increased prevalence of autism diagnoses, the rate of associated Intellectual Disability (ID) tended to decrease. Among ASDs, as the possible cause also the reason of the increased prevalence of autism not yet given us to know, thus it remains unclear.

However, on the basis of recent epidemiological studies, a best estimate of 60 to 70/10.000 (6 to 7/1.000; or 0.6 to 0.7%; or one child in about 150 children) can be confidently derived for the prevalence of autism spectrum disorders (Fombonne, 2009), clearly higher than reported 15 years ago. To support these data, Chakrabarti and Fombonne (2005) showed that the correlation between prevalence and year of publication was statistically significant and studies with prevalence more than 7/10.000 were all published since 1987. These findings point toward an increase in prevalence estimates in the last 15–20 years.

Even though in his classic paper of 1943, Kanner did not propose a direct association between autism and mental retardation, subsequent research established the close and specific relationship between the two conditions. The long-established view of intellectual abilities in autism spectrum disorders (ASDs) was that up to 75% of individuals had an intellectual disability, but this rate first formed several decades ago when conceptualisation of autism, in terms of to whom the diagnosis is applied and how prevalent the disorder is, was very different from today and, thus, historical data might not apply to children who currently receive an ASD diagnosis. To date, indeed, there is evidence from recent epidemiological studies that only approximately 50% of children with ASDs have

intellectual disability (IQ <70) (Bertrand et al., 2001; Chakrabarti & Fombonne, 2005).

However, among Autism Spectrum Disorders (ASDs), IQ was found to be a strong predictor of short- and long-term outcomes, such as a potential moderator of response to treatment strategies. Several researchers have described pretreatment variables that seem to are highly correlated with later outcome. Although findings have not always been consistent, the most commonly, though not always, noted predictors have been IQ (Bibby et al., 2002; Eikeseth et al., 2002).

In light of the above arguments, a specific assessment of cognitive functioning, as soon as possible, should be rigorously performed to obtain an appropriate evaluation of ASD subjects. The clinical need for intelligence quotient information contrasts with no current agreement about the most appropriate test. Several cognitive functions can be tested using the Wechsler Intelligence Scales, the Stanford-Binet Intelligence Scale, and the Mullen Scales of Early Learning; furthermore, for individuals with autism and poor linguistic levels, the Leiter International Performance Scale can be used.

Unfortunately, in the clinical practice, administering IQ tests can be difficult and potentially result in lower scores due to the typical clinical phenotype and behavioral problems. Thus, in young ASD children, the Psychoeducational Profile-3 (PEP-3) represents the most useful and manageable tool for the assessment. Portoghese et al. (2010), in a study evaluating only ASD subjects and at the same time point, showed that all items of the PEP-R DQ scores were significantly related to the total Leiter-R IQ scores. Consequently, all items

significantly contribute to determining the correlation between IQ on Leiter and overall DQ.

Building on existing literature, although most studies to date have been cross-sectional, PEP scores were found to be related to IQ levels; thus, developmental profile could be used to estimate cognitive functioning of preschooler children with ASD.

Therefore, even if cross-sectional studies can be extremely useful for generating hypotheses, these hypotheses need to be further confirmed by longitudinal investigation. Indeed, longitudinal data may provide efficient estimates of change and predictors of change over time as much as identification and characteristics of distinct subgroups defined by change pattern.

2.2 Objectives

The aim of this study was to evaluate the longitudinal cognitive profile from the first evaluation to IQ assessment, trying to answer these three questions: 1) At each time point, does the ASD group show a different developmental profile compare to typically-developing? 2) Is there one or more PEP domains at the first time point related to final IQ level? 3) What is the prevalence of Intellectual Disability in our ASD sample?

2.3 Methods

This investigation was performed at Child and Adolescent Neuropsychiatry Department, University of Catania (Italy).

Sample

61 children and adolescents suffering from ASD and 18 Typically-Developing (TD) matched children were assessed at 3 time points, each 12-24 months apart (mean age at Time 1: ASD=3.4±0.2 years; TD=4.1±0.4 years).

ASD patients have been diagnosed within the spectrum of autistic conditions according to the DSM IV-TR criteria. However, we used the Autism Diagnostic Interview-Revised (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (Lord et al., 1989) as part of the autism diagnostic assessment. IQ was measured with Leiter International Performance Scale–Revised (Roid and Miller, 1997). No qualitative and quantitative differences were detected on treatment strategies among ASD group. None of the subjects had ever used any psychotropic medication.

TD children were randomly were recruited from public elementary schools, in a predominantly middle-class urban community in Catania, Sicily (Italy).

The participants' parents who accepted to take part in the research signed a consent form, and children and adolescents assented to participation.

Measures

The Psychoeducational Profile-Third Edition (PEP-3; Schopler et al., 2005) is a norm-referenced assessment tool designed to evaluate the uneven learning strengths and weaknesses that often characterize individuals on the autism spectrum. It provides information on developmental skill levels and can assist in determining the severity of symptoms related to autism for children from 6 months to 7 years. While it is not a direct measurement of intelligence or general cognitive abilities, the PEP-3 provides helpful descriptive information concerning a youngster's characteristic cognitive pattern, including solving problems, relating to environmental stimuli, and coping with transition between tasks. Six of the 10 subtests are related to broad performance across a variety of tasks, while the remaining four are concerned with adaptive behaviors demonstrated during the testing session. PEP-3 information is particularly valuable when a child is unable to respond to traditional formal cognitive measures.

Leiter International Performance Scale–Revised consists of 20 subtests divided between two batteries, a Visualization and Reasoning Battery and an Attention and Memory Battery (Roid and Miller, 1997). Administration of the test is in easel format, and response items include foam shapes at earlier levels and cards at most levels. The response format generally involves placing a card in the appropriate slot below the easel (or arranging the foam shapes), but it also requires pointing for some subtests. The Leiter-R is normed for individuals between 2 years, 0 months and 20 years, 11 months of age. The Visualization and Reasoning (VR) Battery consists of 10 subtests in all; 4 subtests comprise a Brief

IQ Screener for all ages, and two sets of 6 subtests (one set for children between 2 and 5 years, and a second Concurrent Validity of Leiter and Leiter-R in Autism 25 set for individuals 6 to 20 years) are used to obtain a Full-Scale IQ. There are three composite scores also yielded on the Leiter-R: Fluid Reasoning, which is available for all ages; Fundamental Visualization, obtained for children 2–5 years of age; and Spatial Visualization, available for the 11–20 year age range. IQ and composite scores have a mean of 100 and standard deviation of 15, whereas individual subtest scores are scaled with a mean of 10 and standard deviation of 3. In practice, the test is manageable, and does not require proficiency in perceiving, manipulating, and reasoning with words or numbers, or using any other materials traditionally identified as "verbal". All administration instructions are adapted to a nonverbal format. Because of these features, this scale is widely utilized to assess the intellectual function of children with ASD, especially those who cannot be tested with standard intelligence tests. The Leiter-R scale potentially allows the obstacle of the impaired communication skills, attention, and behavior observed in these children24 to be overcome, albeit not completely.

Procedures

At Time 1 the PEP-3 was used to assess all ASD (mean age=3.4±0.2 years) and TD (mean age=4.1±0.4 years) children to identify skills and behaviors that could be useful for diagnostic and educational planning goals. After this first evaluation two follow-up were performed to all subjects, each 12-24 months apart.

At the first follow-up, 6-12 months later (Time 2), the PEP-3 was readministered to both ASD and TD group.

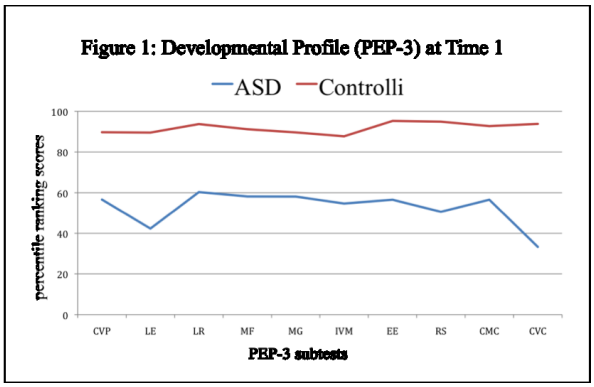
Finally, on Time 3 assessment, conducted 12-24 months after T2, IQ evaluation using the Leiter International Performance Scale–Revised was performed to all participants.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS 14.0 for Windows). Both descriptive and inferential analyses were undertaken. Chi-square analyses for dichotomous variables, and one-way ANOVAs with post hoc Bonferroni multiple comparison t-tests were conducted for continuous variables. Pearson's correlations, and linear regression models were applied to the data in order to evaluate the association between developmental variables and intellectual functioning. An alpha level of .05 was set for statistical significance.

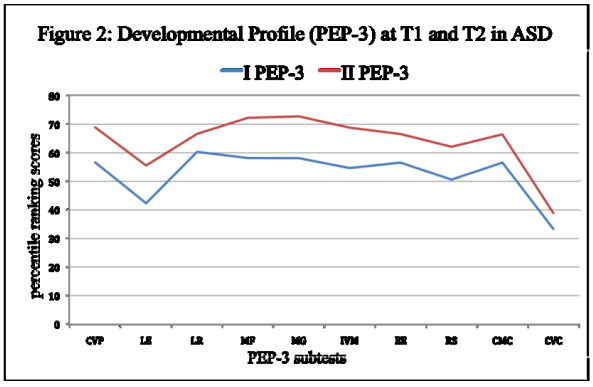
2.4 Results

- Trajectories of developmental profile

At Time 1 all PEP-3 domains exhibited a greater developmental delay in ASD compared to TD, also distinguished for typical disharmonic profile that showed expressive language, visual-motor imitation and social reciprocity as areas of weakness (Fig. 1). At Time 2, on gross motor, visual-motor imitation and affective expression subtests no significant differences were observed between ASD and TD.



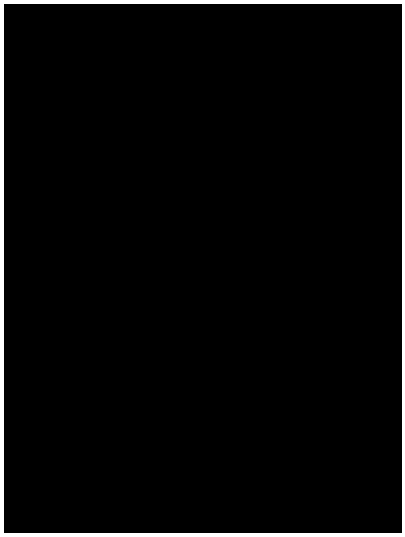
On ASD group, comparing the PEP-3 profile at T1 with that at T2, our preliminary data show an improvement in all subtests; and, even though, most areas remained far back to the typicall average development, the fine and gross scores were within the normal range (Fig. 2).



- Correlation between PEP-3 domains and IQ level in ASD sample

An analysis using Pearson's correlation was used to determine, in ASD group, the relationship between PEP-3 scores and IQ level.

As shown on Table 1, all domains of the PEP-3 assessed at T1 were not found to correlate significantly with Leiter-R IQ scores evaluated at T3.



- Prevalence of Intellectual Disability in our sample of ASD

In our sample of ASD, the prevalence of intellectual disability, defined by an IQ<70, was 29% (mean IQ=88.9±15.7). Of those, the 15% had a moderate or severe impairment on PEP-3 cognitive subtest while the reamining 14% showed a mild difficult on the same domain (Fig. 3).

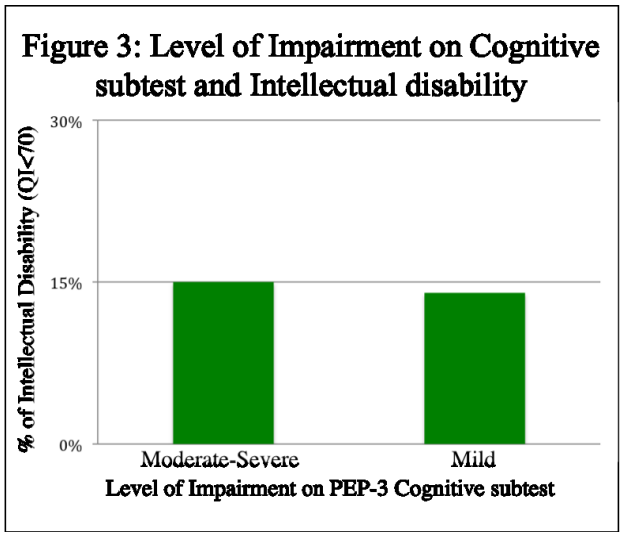


Figure 3: Level of Impairment on Cognitive subtest and Intellectual disability
% of Intellectual Disability (QI<70)
30%
15%
0%
Moderate-Severe
Mild
Level of Impairment on PEP-3 Cognitive subtest

2.5 Discussion

In our study a typical disharmonic profile was found in ASD sample, which consisted of particular strengths and weaknesses, confirming the delay and asynchronism of different skills commonly observed in these disorders (Steerneman et al.,1997, Portoghese et al., 2009). Thus, the PEP-3 represents a useful tool for the assessment of children with ASD, offering the possibility of assessing a wide developmental range. In our sample, all developmental domains were found to be more severely impaired in the ASD group, with expressive language, visual-motor imitation and social reciprocity as areas of weakness. These results confirm an overall and pervasive developmental delay, according to the impairment of specific functions reported in children with autism (Charman et al., 2002; Fombonne, 1999).

Although a typical disharmonic profile could be considered indicative of autism, particular issues should be highlighted in the differential diagnosis of ASD from language impairments. The important longitudinal study of Howlin and coll. (2000) has indicated the long-term social impairments of a group of children originally thought to have only language difficulties, showing that children with specific language impairments not only have difficulty in processing language but may also have difficulty in processing other kinds of communicative information. Moreover, children with receptive language problems may also require adherence to routines and have limited imaginative play skills and peer-based social competence; and, even where there had subsequently been significant progress with language learning, the social impairments remained very significant

(Michelotti et al., 2001). However, specific additional impairments in social communicative features such as social interest, use of pointing, eye-gaze and other non-verbal gestures to regulate attention, impairments in imitation, a peculiar speech pattern and an unusual or bizarre response to the environment are not related to language level and could be used to differentiate these two disorders (Lord & Pickles, 1996).

Moreover, our longitudinal data comparing the developmental profile at two time point 6-12 months apart, show a improvement, even though quantitatively different, in all domains including also the cognitive subtest. According to this finding, Portoghese and coll. (2009) found that cognitive performance was the domain with the most reactions judged as 'emerging' in both groups, suggesting that cognitive functioning may be the domain with the greatest developmental potential in younger children with ASDs.

This is the first longitudinal study, to our knowledge, that examined the relationship between developmental profile domains and IQ level. Despite literature data, in our analysis using Pearson's correlation was not found any significant correlation between these two variables. On the other hand, from results of recent studies comparing developmental scores with IQ, these two variables seem to be significantly related (Delmolino, 2006; Skek et al., 2005; Portoghese et al., 2010). An explanation on why our findings differ from literature data could be related with the fact that most of the clinical studies on this topic are cross-sectional, comparing the two measures at a single time point and at an early development stage, unlike our research which is longitudinal. As yet well-known, in the clinical practice and especially in younger children, administering IQ tests

can be difficult and potentially result in lower scores due to the typical clinical phenotype and behavioral problems.

It has long been recognized that cognitive impairment is a feature often associated with autism. Assessing levels of intelligence in children with autism spectrum disorders is important to be able to understand their ability, to make a reliable prognosis, to plan remedial education, and as an outcome measure in evaluation of treatment effectiveness.

In our sample of ASD, the prevalence of intellectual disability, defined by an IQ<70, was 29% (mean IQ=88.9±15.7). From these results, ASDs seem to be less strongly associated with intellectual disability than traditionally held, according to recent epidemiological data (Charman et al., 2011). Moreover, among this 29% of ASD subjects mentioned above, the 15% had a moderate or severe impairment on PEP-3 cognitive subtest while the reamining 14% showed in the same domain a mild difficult. Consequently, the level of impairment obtained from PEP-3 should not be used as a predictor or an estimate of the intellectual ability of young children with ASDs.

The present study has a number of limitations that must be taken into account in interpreting the data, but one deserves to be highlighted. The cognitive ability cannot be explain simply with a number on an IQ test, but should be account many other underlying cognitive functions. Indeed, the accumulating evidence of behavioral and genetic fractionation of the autistic triad is paralleled by a failure to find a single cognitive account for the three core features of autism. Current cognitive accounts of autism can be divided into those that posit a primary deficit in social cognition (theory of mind, emotion processing or social

orienting) and those that posit a primary deficit in nonsocial or domain-general processing (executive dysfunction, enhanced processing of local features or abnormal attentional processes). Also neuroimaging studies of autism also appear to offer support for the independence of the cognitive substrates for social, communicative and rigid/repetitive impairments.

Even so, the findings of this study can have important implications for both clinical practice and further research because a better understanding of the cognitive level may not only have positive implications for an early diagnosis but also for intervention and long-term outcome, as well as to differentiate cognitive phenotypes in the clinical research.

Finally, I'd conclude this dissertation by asking a question:

"Is there a deficit or a different style cognitive among ASDs people?"

Still do not know.

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This dissertation is dedicated to..

..my father and my mother for the love and support that exceeded my wildest dreams, as a safety street when I could walk forward..

..my irreplaceable brother, I could not have asked for a better friend

..My Professor for all of the support, guidance, and attention he provided always along the way.