

An Italian Prospective Study on Autism Treatment: The Earlier, the Better?

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Abstract

Background: Neurocognitive models of autism suggest that starting a treatment at a younger age might be a critical factor in promoting optimal outcomes. The aim of the study is to examine the relationship between age at start of treatment and outcomes in a group of children with Autism Spectrum Disorders (ASDs) in Italy.

Methods: Thirty-nine children between 22 and 77 months of age diagnosed with ASDs were divided into two groups on the basis of their age at start of a community-based behavioral treatment. Measures of severity of symptoms, cognitive abilities and adaptive functioning were collected at the beginning of the treatment (Time 1) and one year after (Time 2) to examine group differences in treatment outcomes. Our working hypothesis was that children who started the treatment at a younger age would show a more positive response to treatment compared to children who started at later age.

Results: Compared with children who received a diagnosis and started the treatment at a later age, children in the early treatment group showed a better outcome in terms of attenuation of symptoms severity. No group differences were found in terms of adaptive functioning and cognitive abilities, with both groups equally improving their performance.

Conclusions: Age at start of the treatment seems to be an important factor to promote gains in the social-communication domain. However, gains in adaptive functioning and cognitive skills in our sample were not related to age. The positive effect of a community-based intervention in children with an early diagnosis of ASDs might be due to the plasticity of neural systems in age-dependent stages. The possibility that early intervention could substantially alter the course of behavioral and brain development in children with autism points to the urgent need for more research on treatment in this population.

Keywords: Autism Spectrum Disorders; Early diagnosis and treatment; Cognitive and behavioral outcomes

Introduction

Autism spectrum disorders (ASDs) constitute a class of severe neurodevelopmental conditions caused by atypical brain development beginning during early prenatal life. Etiology is multifactorial, involving a strong genetic underpinning [1]. ASDs are considered to be life-long conditions, with core symptoms being permanent across the lifespan. Currently, no treatments have been proven to completely reverse the core symptoms. Autistic features begin to be evident in children between 12 and 18 months of age, with limitations in joint attention, eye contact, reciprocal smiling, play skills and imitation, and a reliable diagnosis of ASDs can be as achieved by 20 months of age [2-4]. The progress in the detection of autistic disorders has promoted earlier interventions, which have contributed to more positive outcomes for individuals with ASDs [5]. Theoretical foundation for early treatment is based on the notion of early brain plasticity, with research showing that the structure and connectivity of the brain are particularly "open to change" during early childhood. The possibility that early intervention could substantially alter the course of behavioral and brain development in children with autism points to the urgent need for more research on treatment in this population [5-7].

The aim of the current study is to examine the relationship between age of diagnosis and treatment and positive outcomes, as defined by attenuation of autistic symptoms and gains in cognitive and adaptive skills, in children who underwent the same type of intensive behavioral treatment at different ages. Our working hypothesis was that children who started the treatment at a younger age (22 to 48 months) would

show a more positive response to treatment (resulting in attenuation of autistic symptoms and gains in cognitive and adaptive skills) compared to children who started the treatment at a later age.

Methods

Participants

Thirty-nine children between 22 and 77 months of age diagnosed with autistic disorder (AD) or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) in our clinic were selected for our study. Inclusion criteria were 1) age between 22 and 77 months, 2) and meeting criteria for an ASD based on the Autism Diagnostic Interview Revised (ADI-R) [8] and the Autism Diagnostic Observation Schedule (ADOS) [9].

Exclusion criteria included (1) neurodevelopmental disorders of known etiology (as Fragile X Syndrome, Tuberous Sclerosis, chromosomal abnormalities) (2) history of regression and/or neurological disease (3) significant sensory or motor impairment (4)

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	Early Treatment (n=19)		Late Treatment (n=20)		t-test p value
	Mean (SD)	Range	Mean (SD)	Range	
Chronological Age	37.7 (7.1)	22-46	58.8 (9.1)	47-77	>.001
Gender	17 M, 2 F		17 M, 3 F		
VABS Age equivalent (composite)	156.44 (82.5)	51-387	242.25 (100.4)	56-619	.03
PEP-R	.51 (.15)	.34 - 1	.53 (.17)	47-77	.78
ADOS CSS	7 (2)	1-9	5.8 (2)	1-10	.08

Table 1: Characteristics of Early and Late Treatment Participants

chronic serious diseases (5) use of psychoactive drugs and (6) severe mental retardation (IQ < 35).

All children also underwent a defined medical workup including neurological examination; awake/sleep EEG, standard genetic analysis and auxological measures. A psychological evaluation involving cognitive and adaptive assessments was also conducted (see below). All children started a community-based intervention (see below) immediately after receiving their diagnosis. For the purpose of our study, participants were assigned to two groups in accordance to their age at the diagnostic evaluation. The two samples were composed by nineteen children in early treatment group (ET) and twenty children in the late treatment group (LT). The mean age at start of treatment was 37 months for the ET group and 58 months for the LT group. The baseline characteristics of the two groups are described in Table 1.

Instruments

The research protocol involved the administration of (1) the Psychoeducational Profile Revised (PEP-R) [10] to determine developmental level, (2) the Vineland Adaptive Behavior Scales (VABS) [11] to assess adaptive functioning and (3) the Autism Diagnostic Observation Schedule (ADOS) for measuring the severity of autistic symptoms.

We administered the PEP-R to determine developmental quotient (DQ) at Time 1 (pre-treatment evaluation) and Time 2 (post-treatment evaluation, one year after treatment started). The PEP-R is widely used in clinical settings and its utility has been extended to research work to describe clinical features and to investigate treatment outcomes. Although the PEP-R was not originally designed to determine general level of intellectual functioning, several studies have suggested that the PEP-R provides a good estimate of cognitive abilities in young children with autism and/or other disabilities and a sensitive pre-post measure for treatment outcomes evaluation [12-14].

To test participants' gains in everyday life adaptive skills, we administered the VABS. The VABS are the most widely used instrument to assess adaptive functioning in both clinical settings and research protocols. Domains covered by the Vineland include Communication, Daily Living Skills, and Socialization.

The ADOS was also administered to ascertain diagnosis and determine severity of symptoms at Time 1 and Time 2. Module 1 (minimal to no language) or 2 (non-echoed phrase speech) was given, according to the children's language level. A standardized severity score based on codes within the domains can be calculated to compare autism symptoms across modules. The calibrated severity score (CSS) allows for a comparison of scores across distinct algorithms and it is also useful for providing a more specific measure of outcome in treatment/ or clinical trials [15].

Procedures

All patients were administered the above mentioned tests by experienced examiners at baseline (Time 1) and one year after their first evaluation and the beginning of treatment (Time 2) in our clinic. Evaluators were blind to the study hypotheses. At Time 2, parents also completed a detailed, non structured questionnaire on the type and modality of interventions received by their children.

The modality of community-based treatment was based on the Italian guidelines on ASD management, and included evidence-based behavioral strategies to improve social-communicative abilities implemented in pre-school and school settings as well as speech therapy conducted in specialized centers [16]. All children received in average 20h of treatment per week.

Results

To test the study hypothesis, we compared the gains achieved by participants in the two groups with respect to adaptive functioning, developmental level, and severity of symptoms (ADOS).

Adaptive Functioning

Each participant's performance on the Vineland Composite Total score at Time 1 and Time 2 was submitted to a 2 (Groups) X 2 (Time) repeated measure ANOVA. There was a main effect of Time: both the ET and the LT group had significantly higher score at Time 2 compared to Time 1: $F(1, 31) = 44.61, p < .001$. However, there was no group by condition interaction, $F(1, 31) = 0.34, p = .56$: both group equally improved their performance at Time 2 compared to Time 1, with no advantage for the ET group over the LT group. Analyses of the Vineland subscales revealed a similar pattern, with both groups equally improving their performance after 1 year of treatment.

Developmental Level

In the same manner, each participant's performance on the PEP 3 at Time 1 and Time 2 was submitted to a 2 (Group) X 2 (Time) repeated measure ANOVA. There was a main effect of Time, $F(1, 31) = 29.03, p < .001$, showing that both the ET and the LT group had significantly higher score at Time 2 compared to Time 1. No significant Group by

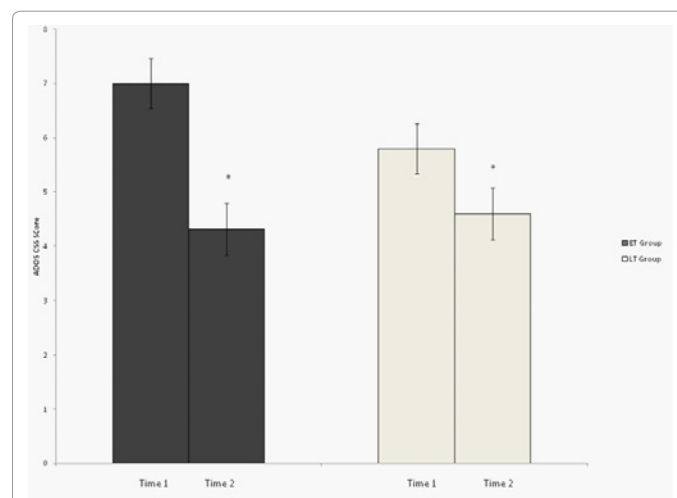


Figure 1: Both the Early Treatment (ET) and Late treatment (LT) groups significantly improved in terms of PEP-3 Developmental Quotient (DQ) score at Time 2 compared to Time 1, with no statistically significant advantage for the ET group.

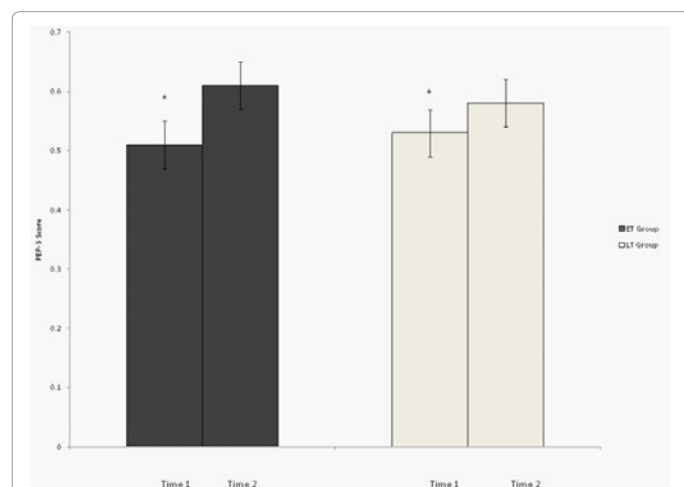


Figure 2: Both the Early Treatment (ET) and Late Treatment (LT) groups showed a decrease of ASDs symptoms severity at Time 2 compared to Time 1. However the ADOS scores decreased significantly more in the ET group compared to the LT group.

Time interaction was found, $F(1, 31) = 1.05, p = .31$. Again, both group equally improved their performance at Time 2 compared to Time 1, with no advantage for the ET group over the LT group (Figure 1).

Symptoms Severity

Each participant's performance on the ADOS calibrated severity score was submitted to a 2 (Groups) X 2 (Time) repeated measure ANOVA. We found a main effect of Time, with both groups showing less severity of ASD symptoms at Time 2 compared to Time 1: $F(1, 37) = 33.10, p < .001$. A Group by Time interaction was also found, $F(1, 37) = 4.83, p < .05$, indicating that the ET group improved more than the LT between Time 1 and Time 2 group in terms of attenuation of symptom severity (Figure 2).

Discussion

Results of this study show that children who started the treatment at a younger age show a more positive response to treatment compared to children who started at later age. In terms of adaptive functioning and developmental level, we found that both group equally improved their performance at Time 2 compared to Time 1, with no advantage for the ET group over the LT group.

Although early diagnosis of ASDs are generally stable over time, recent researches focused on a subset of children who are diagnosed at young age and eventually lose this diagnosis [2,4,17]. Several studies have confirmed a positive relationship between intensity of the treatment and positive outcome, in term of better cognitive and adaptive skills and, in some cases, less severity of symptoms [18-20]. Consistently with previous literature [21-24], findings from the present study indicate a significant association between early beginning of therapy and clinical improvement, supporting the idea that an early identification and treatment in very young children with ASDs is needed for achieving an optimal outcome [25,26]. Nevertheless, it is very important to mention that children in the LT group also underwent clinical improvements in terms of adaptive functioning and cognitive skills. This finding points to the importance of providing intensive treatment to children with autism at any age.

The positive effect of a community-based intervention in children with an early diagnosis of ASDs might be due to the plasticity of neural

systems during that time. Brain plasticity refers to the ability of the nervous system to change under genetic and environmental forces. Before birth, brain development is almost exclusively under genetic control and the genome guides all the initial growth and differentiation of nervous cells and synapses formation; after birth, learning and experience become major influences of neuronal growth and synapse development, in age-dependent stages [27].

Animal studies have demonstrated that early environmental enrichment can mitigate the effects of genetic and environmental risk factors on brain and behavioral development. Environmental enrichment has been shown to directly affect brain development and neural plasticity in animals, with increased numbers of synapses and molecular changes, including modulation of the genetic expression of neurotransmitter pathways and increased neurotrophic factors [28]. Early intervention can also provide the stimulation for the development of efficient neuronal circuits that are probably less robust in ASD. Symptoms of ASD are linked to dysfunctions in the structure and connectivity of specific brain regions, including the posterior cingulate cortex, lateral parietal cortex/angular gyrus, medial prefrontal cortex, temporal lobe, and parahippocampal gyrus [29]. Moreover, deficits in the formation of brain circuits associated with a lack of "pruning" of local brain circuits result in overconnectedness within these systems, thereby leading to disorganization at the local level. The diminished capacity of long-range circuitry formation may determine impairments in the integration of complex brain functions and in the development of complex skills that are deficient in ASDs [30]. Thus, early training of learning is the key to producing the essential neuronal circuitries.

These evidences raise the possibility that early interventions can substantially change the course of both behavioral and brain development of children with ASDs. In this view, treatment should begin during the period of maximal receptiveness and plasticity of the brain, as at age of 1 to 5 years. After about 6 years of age, CNS plasticity is reduced by complex neurobiological mechanisms of active inhibition, such as reduction of myelin and inhibition of axon growth. Moreover, the social and communicative impairments caused by ASD may progressively determine a cascade of clinical and neurobiological abnormalities toward full expression of the disorder. Consequently, the effectiveness of treatment may be reduced with the advance of children age. So, even if ASD have a highly genetic base, mechanisms of brain plasticity can facilitate achievement of optimal outcome through an intensive and early intervention.

A goal for the future is to demonstrate that very early intervention results not only in significant improvements in behavior, including reduced autism symptoms and increased cognitive, language, and social abilities, but also in significant changes in brain function and organization. A more comprehensive understanding of the neurobiological mechanisms responsible for effective intervention can open the door to the first prevention of ASDs.

There are limitations to the present study. First, the sample of children is small, and caution should be taken when generalizing these results to the broader population. A larger sample would allow for a more fine-grained analysis of predictors of outcome. Moreover, one year of follow up obviously can not constitute a final developmental outcome. It will be necessary to follow the ASD cohort to monitor the gains and the stability of the diagnosis over time. Additionally, the relationship between intervention variables and pre-treatment child characteristics is likely to be very complex and they will be analyzed in future studies to determine the impact of intensity, type, and setting of service on outcomes.

Key Points

Current theories on autism suggest that starting a treatment at an early age might be a critical factor in promoting optimal outcomes.

In our sample, children who started the treatment at a younger age showed a more positive response to treatment compared to children who started at later age.

Both group equally showed improvements in their adaptive and cognitive with no advantage for the Early Treatment group over the Late Treatment group.

Our data partially support the idea that children who start their treatment at a younger age will show more gains than children who start at a later age.

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