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Title: Clinical outcomes of interactive, intensive and individual (3I) play therapy for children with ASD: an open exploratory study

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Abstract:

Background: The outcomes of psycho-educational interventions for Autism Spectrum Disorders (ASD) comorbid with severe to moderate intellectual disability (ID) are

insufficiently documented. In this prospective study, we examined a developmental, Individual, Interactive and Intensive approach, called the '3I method', based on play therapy.

Material and methods: Twenty DSM-4R ASD subjects (mean chronological age=63.8 ± 37.8 months; mean developmental age=19.5 ± 6.6 months) were included and followed the 3I method for 24 months. Developmental and behavioral skills were assessed at baseline and after 24 months using the VABS, the PEP-R and Nadel Imitation scale, and autism severity was evaluated using the Child Autism Rating Scale (CARS) and the Autism Diagnostic Interview (ADI-R).

Results: After 2 years of the 3I method, our 3 primary outcome variables significantly increased (VABS developmental age of socialization by 83%, age of communication by 34%, and Nadel Imitation score by 53%). Almost all VABS and PEP-R domains significantly improved. Additionally, increases in VABS socialization score were positively correlated with the total number of hours of treatment and CARS score; all ADI-R areas significantly decreased; and diagnoses had changed in 47.5% of the subjects (37% for PDD-NOS and even 10.5% for non-PDD).

Conclusion: Children who followed the 3I method for 2 years had significantly improved behavioral and developmental skills and showed a clear decrease in autism severity. These results suggest that the 3I method may be useful for autistic children, improving their daily interactions with their social environment.

INTRODUCTION

Autism spectrum disorder (ASD) is a life-long neurodevelopmental disorder characterized by early impairments in socio-communicative skills that are associated with a set of restricted interests and/or repetitive stereotypical behavior (American Psychiatric Association, 2013). Recently, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM V) added sensory impairments to the diagnostic criteria of the behavioral manifestations of ASD (Lainé *et al*, 2011; Barthelemy *et al*, 1990; Adrien *et al*, 1995). Many research efforts have been made to identify precursors of ASD, leading to a significant decrease in the age of diagnosis (Voineagu & Yoo, 2013), which enables earlier treatment. The existing treatments are mainly symptomatic.

Behavioral methods, which aim to develop certain expected behaviors through child reinforcement, have been proposed to treat ASD with significant scientific support (Kasari *et al*, 2012; Eikeseth, 2009). Applied Behavior Analysis (ABA) is a one-to-one intensive approach based on behavioral strategies and targets specific symptoms using reinforcement of adaptive, expected skills (Vismara & Rogers, 2010; Eapen *et al*, 2013). After criticisms regarding the lack of spontaneity in this early approach, Pivotal Response Training was subsequently developed and uses children's own choice of games and activities to reinforce the correct answers expected by the professional; this type of training also favors providing complete or incomplete forms of attempts to respond, alternating between acquisition and maintenance, and using intrinsic reinforcers (Koegel *et al*, 2001). Additionally, the Treatment and Education of Autistic and related Communication handicapped CHildren (TEACCH) program emphasizes a close working relationship between parents and practitioners, adapts

the intervention to the characteristics of the child and uses structured teaching educational techniques (Virues-Ortega *et al*, 2013).

Alternatively, ***developmental approaches*** start from the specific interests and resources of the child and aim to restore the global developmental process to increase communication skills and learning ability. One example is the Son-Rise Program®, developed in the early eighties, which was essentially based on "joining" the child, playing with him and following his cues. This program has been followed by tens of thousands of families in the U.S.A., and a recent study based on 5 days of intensive treatment of 6 children showed encouraging results (Houghton *et al*, 2013). Other developmental interventions based on play therapy have conceptualized the relationship between playing and child development, such as Floor Time (Greenspan, 1997; Pajareya & Nopmaneejumruslers, 2011) or in France, "Exchange and Development Therapy" (EDT), which was developed in the 1990s by Lelord (Blanc *et al*, 2013). Floor Time consists of sequences of guided play (15–20 min) that are repeated several times by parents throughout the day and are supervised by an expert. Floor Time is the core of the Developmental, Individual Differences, and Relationship-based (DIR) method. DIR focuses on individual developmental differences in a child's emotional functioning, information processing, motor planning and types of interactions. The DIR method recommends following the child's lead and supporting his/her initiative; focusing on joint attention; closing circles of communication; creating semi-structured problem solving approaches; contrasting repetitiveness with playful obstruction; supporting visual attention; and working on imitation (Wieder & Greenspan, 2003; Pajareya & Nopmaneejumruslers, 2012).

Some methods mix elements of developmental play therapy with a structured and behavioral teaching approach**.** The Braintraining method (Mac Alpine, 1999; Kaye, 2012) associates

guided play time with teaching material depending on the specific developmental stage of the child's playing ability. Multi-sensory activities help increase the child's level of multimodal integration, overcoming difficulties that would restrict the development of more sophisticated cognitive skills such as symbolic play, language and social understanding. The Early Start Denver Model (ESDM) is an early and intensive intervention approach for young children that combines developmental and behavioral approaches. This method was evaluated in a randomized control trial with 48 toddlers (Dawson *et al*, 2010), and the study showed that ESDM effectively improved cognitive and adaptive behavior and reduced the severity of ASD diagnoses. A complementary electro-physiologic study suggested that a certain normalization of brain function was associated with clinical improvement (Dawson *et al*, 2012). In recent years, the ESDM has aroused great interest; for example, a study on at-risk infants suggested increased developmental abilities and a decrease in autism severity after three years of ESDM treatment (Rogers *et al*, 2014). Some behavioral therapists have also tried stimulation with small children using their favorite games and activities and showed a sustained improvement in social interactions (Koegel *et al*, 2014). Thus, the concept of triggering developmental processes in children with ASD has advanced in the scientific community.

In France, health facilities often provide institutional approaches to develop relational skills through various activities and therapeutic mediations, in groups or individually (Poinso *et al*, 2013). These approaches have increasingly been associated with structured tools from an integration perspective; for example, the ESDM has recently been integrated into the French health care service (Schröder *et al*, 2015). A previous review highlighted the diversity of practices in France but also the lack of published data on the effectiveness of these institutional strategies (Pry *et al*, 2007). A French multicenter study is currently underway to evaluate the effectiveness of an integrated, individual, intensive structured teaching program

provided to children with ASD and moderate intellectual disability (ID) in institutional care (Tanet *et al*, 2016).

Beyond the diversity of individual approaches, an analysis of the literature has provided some important guidelines for improving the treatment of ASD children (Narzisi *et al*, 2014), including the following: i) Diagnose and start interventions early; ii) provide at least three or four hours of treatment each day; iii) center interventions on family involvement, placing parents in a position that allows them to actively participate in the education of their child; iv) provide regular updates on progress and subsequent goals; v) choose between behavioral or developmental treatment depending on the child's response; vi) encourage spontaneous communication; vii) include interactions with peers as soon as possible; viii) help extend the acquired skills to various environments and natural contexts; and ix) support positive behaviors rather than tackling challenging behaviors (Narzisi *et al*, 2014; Pry *et al*, 2007). Notably, previous studies suggested that involving the family in the treatment of the child promoted the therapeutic effect. For example, in a French study on a 20-month home-intensive method involving the family, 25 children progressed from 6 to 25 points in their developmental quotient (Gattegno, 2008). In addition, a randomized controlled Australian study showed that parental involvement through home-specific work promoted the efficiency of treatment (Rickards *et al*, 2007; Green *et al*, 2010). Similar results, showing beneficial effects of parental contribution in early intervention, have been published and highlight the importance of parental involvement in treating ASD (Green *et al*, 2010; Venker *et al*, 2012; Wetherby *et al*, 2014), even for long-term outcomes (Pickles *et al*, 2016).

In this study, we examined a developmental, Individual, Interactive and Intensive approach to treat ASD comorbid with ID called the '3I method', which was based on the playing ability of

the child and included the family. As this play therapy was meant to stimulate developmental processes, the child's progress was analyzed by a psychologist through regular team meetings, considering the normal developmental pattern of a child of his/her developmental age. Here, we present a prospective exploratory study that aims to assess the outcome of 20 ASD subjects who followed the 3I method for 24 months. Using appropriate scales, we estimated the course of developmental and behavioral skills and autism severity after two years.

Material and methods

Participants - Ethics

The protocol of the study was approved by the institutional ethical committee and was registered by the French Agency for drug and health (ANSM) under number B148558-31. All parents of the subjects spontaneously contacted the *Association Autisme Espoir vers l'Ecole* (AEVE) to help them provide 3I treatment to their children. They voluntarily provided informed consent to include their child in the study after being informed of the study design and goals.

The inclusion criteria were as follows: being diagnosed with ASD based on the Autism Diagnostic Interview, Revised (ADI-R) and the Childhood Autism Rating Scale (CARS); starting the 3I method from January 2013 to December 2013; residing in an environment that allowed for the correct application of the 3I method; not receiving any other ASD intervention treatment method (*e.g.,* ABA or TEACCH); and having French as their maternal language. The exclusion criteria were as follows: the presence of associated diseases such as epilepsy or Rett syndrome; Asperger syndrome; and inability to ensure 3I treatment for the entire duration of the study. Patients aged > 15 years old at the beginning of the study were not included.

During the one-year selection period (January to December 2013), 31 children started the 3I program, but only 20 were included in the study. Four of the eleven remaining children were outside the age range (too old), three presented Asperger syndrome, two suffered from epilepsy, and two could not receive intensive 3I treatment. All the included subjects were not attending school and followed the 3I method for between 30 and 35 hours per week. Specifically, 17 children followed the 3I method at home, and 3 at the AEVE Courbevoie day center. The patients' age at the beginning of the study ranged between 2.8 and 14.5 years.

3I method

The 3I method is promoted by AEVE, a nonprofit association founded in 2006. The 3I method is derived from the SonRise® Program but has important differences. As with SonRise®, the intervention occurs in a specific room devised for a one-to-one interaction and designed to reduce unwanted sensorial stimuli. The basic intervention principles are also the same and are directed towards "joining" the child's world without any expectations through playful reactions to the child's cues (Thompson & Jenkins, 2016). However, the 3i method i) focuses on the sensory specificities of the child as well, ii) provides participants with a developmental roadmap that improves understanding of the present abilities and difficulties on their developmental path, and iii) distinguishes three developmental age stages in their corresponding agenda (0 to 18 months, 18 to 36 months and over 36 months, Gardziel *et al*, 2015).

The 3I Method presents important similarities with Exchange and Development Therapy (EDT), which is practiced in France and is based on approximately two sessions of 45 minutes each week (Blanc *et al*, 2013). The key aspects of this therapy are as follows: i) a quiet

environment, to limit excessive neural reactivity in the child to sensorial stimuli, ii) openness of the therapist, lack of expectations, and careful observation, and iii) facilitation of reciprocity by, for instance, free imitation (Nadel & Potier, 2002).

However, the 3I method is recommended to be intensive: a minimum of 30 hours of play sessions is proposed per week and in a specific playroom. Each game session lasts 1 and a half hours. The recommended size of the playroom is around 10 sq.m., which offers a space with boundaries visible by the child. The lighting must be subdued, and the sounds should be muffled with appropriate ground lining. The standard equipment in the room includes shelves out of the child's reach where objects will be visibly stored, a mirror, a swing and a few other items used to gain a physical perception of oneself; these items can be visual such as clay, tactile such as color cubes, and auditory such as a triangle or xylophone, as well as picture books, puppets, etc. Sessions are provided by volunteers. These participants are mostly non-professionals in the field of ASD. They undergo a preliminary screening and receive an initial training by a 3I method expert before starting to interact with the child in the playroom. They subsequently participate each month in a group session with the other participants, together with the parents, under the supervision of a trained psychologist. For each child, a 3I-trained psychologist manages the team of volunteers and ensures the consistency of their actions and their compliance with the 3I method. The child's progress is recorded and analyzed by the psychologist, who provides some advice according to the participants' questions and the child's evolution.

The 3I intervention is organized into three phases, which correspond to the developmental age brackets of 0 to 18 months (Phase 1), 18 to 36 months (Phase 2), and over 36 months (phase 3). During phase 1, the intervention is centered on simple sensorial games and

exchanges, without recourse to many objects. The aim is to help children discover themselves, their body and the distinct existence of another person. During phase 2, the child's attention is brought to the external world outside the playroom, a meaningful language emerges, and the child gains access to symbolic play. The child's desire for actual conscious learning appears in phase 3 and leads to progressive integration into a classroom as a classmate, without being seen as a handicapped child.

Clinical variables

Three variables were chosen as the primary measures: developmental age in the Vineland Adaptive Behavior Scale (VABS) communication and socialization scores and the Nadel imitation scale (NIS) score (Scarpa *et al*, 2012). The secondary outcomes were the developmental ages of imitation and verbal communication according to the Psycho-Educational Profile – Revised (PEP-R) scale and the severity of autism according to the CARS. The ADI-R was also used to assess diagnosis status and eventual changes.

The VABS is a measure of adaptive behavior (Sparrow *et al*, 1984) that was used here to assess the impact of the 3I method on the development of socialization, communication, and autonomy in everyday life. The results of evaluations are expressed in months of developmental age. The NIS (Scarpa *et al*, 2012) was added as a primary variable because we aimed to include children with severe intellectual disability as well (developmental age > 18 months), for whom the NIS is better suited, as imitation is a very early skill in development. The NIS provides preverbal communication scores, with a focus on imitation. It contains three items: spontaneous imitation, recognition of emulation and imitation on request. An analysis of the scores obtained in the three evaluation times (T0, T1, T2) offers finer monitoring of the

impact of the 3I method on the development of non-verbal communication, particularly in very young or nonverbal subjects.

The PEP-R test is used to calculate the patient's developmental age at different evaluation times in the following developmental areas: imitation, perception, fine motor skills, global motor skills, oculo-manual coordination, cognitive performance, verbal cognition and behavioral observations according to (Schopler & Reichler, 1994). A developmental age can be calculated for each of these areas. In this study, we specifically focused on the imitation and verbal cognition developmental ages, as they were deemed more significant prerequisites of successful school (re)entry.

The ADI-R is a diagnostic assessment tool based on the description and history of the patient that analyzes his/her development in three areas: quality of social interactions, communication and language, and restricted interests and stereotyped behaviors (Lord *et al*, 1994).

The CARS is used to characterize the intensity of autistic disorder and its evolution during treatment (Schopler *et al*, 1980). The 15 items assessed are typically disrupted in autism and are as follows: social interaction, imitation, emotional response, body use, use of objects, adaptation to change, visual responses, auditory responses, taste-smell-touch (and answer mode exploration), fear and anxiety, verbal communication, nonverbal communication, activity level, intellectual level and homogeneity of intellectual functioning; finally, a global perception of the subject is generated.

Study design

Evaluations were conducted at the usual treatment location. Developmental and behavioral skills assessments with the PEP-R, VABS and NIS were performed by the authors through an

observation session and a parental interview within a month after the first day of treatment (T0), 1 year after the beginning of treatment (T1) and finally 2 years after the beginning of treatment (T2). In addition, the severity of the autistic syndrome was evaluated through the ADI-R (parental interview administered by 3 external psychologists not working with the child) and CARS (some by external psychologists, others by the psychologist who supervised the method) at the beginning (T0) and end of the study (T2) (Table 1).

In the 2-year follow-up, the total duration of participation (patient and parent) in the specific assessments was approximately 22 hours. The evaluations occurred in the child's usual playroom and in a place suitable for parental interviews. To optimize the evaluation sessions, the playroom was designed to exclude anything that could distract the patient during the assessment (slide, swing, mirror, etc.). The playroom was equipped with only two chairs and a table, two cameras on tripods and the evaluation materials.

Statistics

Three subjects left the study before undergoing the T2 tests for the VABS, PEP-R, NIS, CARS and ADI-R. The T2 missing values were inferred by replacing their T2 with T1 values in accordance with the "Last Observation Carried Forward" method (Hamer & Simpson, 2009). The low data homogeneity and small number of subjects implied the use of non-parametric tests to assess differences between the three evaluation times. Multiple comparison of paired measures was performed with Friedman's test. Post hoc analysis (to determine which group of measures differed from the others) was performed if the Friedman test was positive with Bonferroni correction. P-values were considered significant at $p < 0.05$. Statistics analyses were performed using R software version 3.2.1.

Results

Subjects

Twenty subjects were included in the present study between January 2013 and March 2014. All participants were diagnosed with ASD according to DSM-IV criteria. More specifically, according to the ADI-R scores, all subjects met the criteria for autistic disorder (Lord *et al*, 1994). Boys represented 90% (18 out of 20) of the study sample (Table 2). Chronological age at the starting point varied between 33 and 173 months. However, the developmental ages calculated with the PEP-R test were more homogeneous, with a medium developmental age of 19.5 ± 6.6 months (lower 13, maximum 38). Additionally, 65% (13 out of 20) of the subjects were initially categorized as nonverbal with regard to their mode of communication. Overall, the subjects spent 2832 ± 550 hours following the 3I method during the 2 years of their study period. This means that every patient had an average of 4 hours of 3I sessions per day. All twenty subjects completed the baseline and the first year's evaluations (T0 and T1). Three subjects dropped out after one year. One was placed by his parents into a medico-educative institution due to substantial progression. One patient dropped out because the parents rejected pursuit of the 3I method at home. The last patient was lost to follow-up.

Developmental and behavioral skills

All 3 principal outcomes increased significantly during the 2 years of the 3I method (Table 3, Figure 1). The developmental age of communication according to the VABS increased significantly from 15.8 ±9.0 to 21.7 ± 11.2 months, representing a 34% increase. Additionally, the developmental age of socialization according to the VABS increased significantly from 12.8 ± 6.5 to 24.3 ± 13.4 months, representing an 83% increase after 2 years of the 3I method. The

NIS score increased significantly by 53%, which is consistent with the 67% increase after 2 years of the 3I method in the PEP-R imitation developmental age (6.8 months). The PEP-R verbal cognition score increased by only 23% after 24 months, which was not significant.

Additionally, of the 8 other items covered by the VABS and PEP-R evaluations, all increased significantly during the 24 months of the study, except for PEP-R global motor skills (table 3). The overall results suggest that 24 months of the 3I method was associated with a global increase in developmental and behavioral skills among our 20 subjects

ASD severity

In addition to developmental and behavioral skills, we assessed variation in ASD severity using the CARS and ADI-R with 19 patients (unfortunately CARS and ADI-R data at T1 and T2 are absent for one patient) (table 4 and figure 1). Based on these results, the mean CARS score dropped significantly from 44.4 ±5 to 33.7 ± 5.1 at the end of the two years. A CARS score > 37 indicates severe autistic disorder; a score between 30 and 37, slight to moderate autistic disorder; and scores under 30, patients who are outside the ASD range. Based on this scale, 94% of our patients were considered severely autistic at the beginning of the study and 6% moderately autistic. At the end of the two years, only 21% (4/19) remained severely autistic, 53% (10/19) had progressed to a moderate autistic score, and 26% (5/19) could be considered to no longer have autism (Figure 2A). In addition, all ADI-R areas (interaction, communication, and stereotypy) significantly decreased during the 24 months of treatment (table 4 and figure 1). According to the ADI-R, 9/19 (47.3%) subjects had an improved DSM-IV diagnosis. Seven subjects' diagnoses changed from autistic disorder (AD) to Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), and 2 subjects were no longer categorized as having PDD. All individuals still had moderate to severe intellectual disability at the end of the study.

Prediction of outcomes

To test whether any baseline variables correlated with the developmental and behavioral skills evolution and decrease in ASD severity observed, the correlations between each of the 3 principal outcome variables were tested with the following: the patient's chronological age at the beginning of the study, the developmental age (based on the PEP-R) at the beginning of the study, the developmental ratio (developmental age/chronological age) at the beginning of the study, the total duration of treatment and the CARS and ADI-R scores at the beginning of the study. Only the total duration of the treatment was positively correlated with the VABS socialization score (Figure 2). This latter result suggests that a greater number of hours of treatment predicted better improvement in VABS socialization score.

Discussion

Our sample consisted of a population of children who are rarely studied, as they presented severe ASD (mean CARS= 44.5, table 1) with moderate to severe intellectual disability (mean developmental quotient based on PEP-R= 35.3 +/-13.1) at the start of the study. In fact, numerous studies choose to exclude children with a developmental quotient (DQ) below 35 (Dawson *et al*, 2010). Our results showed that after 24 months of the 3I method, our sample of 20 patients globally progressed in different skills: socialization, communication, perception and imitation. In line with these developmental changes, the severity of ASD significantly decreased: after 2 years of treatment, 26% of subjects moved below the CARS threshold proposed for ASD (Table 4). Accordingly, several ADI-R diagnoses changed: while all patients were initially diagnosed with autistic disorder (AD), after two years of the 3I method, 9 out of

19 (47%) had an improved diagnosis. These results appear to be encouraging, in particular because of the relatively high age of the subjects and the lower cognitive profile (mean DQ=35) compared to well-designed randomized trials previously published (eg : Dawson *et al*, 2010).

Interestingly, the VABS socialization change ratio was positively correlated with the total duration of receiving the 3I method. This correlation may indicate one major effect of the 3I method. This variable was the only principal outcome that continued to significantly increase in T2 compared to T1. Indeed, the 3I method involves the use of multiple volunteers interacting several hours a day with the child. This intensive relationship may increase the socialization of the subjects in proportion to the hours spent in the playroom. This result may highlight one of the major interests in methods for treating ASD children.

In contrast, no correlation between the subjects' age and the overall decrease in ASD severity/diagnosis or their progress in developmental skills was found. This result suggests that chronological age is not a primary determinant of success or failure in the 3I method.

Specificities and prospects for education. A progression to higher scores in our sample was observed in VABS socialization (90% mean increase), PEP-R imitation (+61%), Nadel imitation (+49%) and ADI interaction (-45%). These results are consistent, as socialization, imitation and interaction are domains that appear to be directly or indirectly linked. Interestingly, although these children had not been "socialized" at school, the greatest improvements were observed in socialization. Peer-to-peer immersion is thus not the only way to "socialize", and an alternative method could be to improve interactive and relational functioning in a privileged system with responsive adults before joining the school system. This suggests that first acquiring the ability to be in a relationship, before learning how to adapt to peers and an

institution, may be beneficial for ASD patients. This is the specific aim of AEVE, to promote socialization and communication of ASD children to allow them to integrate into a regular school system.

In terms of play therapies and the 3I method, Gardziel *et al.* previously commented on the positive aspects of the 3I method and described its beneficial effect on one ASD patient (Gardziel *et al*, 2015). In another study, the progress of 3 ASD patients treated with the 3I method was assessed using the BECS, PEP-3 and CARS (Le Guen & Brengard, 2014). After two years of receiving the 3I method, the 3 children showed a positive evolution: they had less invasive autistic disorders and communicated and interacted more with others. The present prospective study shows for the first time the potential benefit that ASD patients could receive from intensive play therapy with the 3I method. These results are in line with those of other studies on play therapy: Floor Time (Pajareya & Nopmaneejumruslers, 2011, 2012), "Exchange and Development Therapy" (Blanc *et al*, 2013), and SonRise (Houghton *et al*, 2013); ESDM also partially uses play therapy components. All these play therapy methods share a developmental vision in which the child can succeed in building relational abilities through repeated experiences in individual relationships with responsive, joyful and empathic adults . This dyadic context may be crucial for the development of the first stages of relational abilities.

Another interesting point is the importance of including parents in therapy. As mentioned in the introduction, some studies have reported a positive impact of parental participation (Rickards *et al*, 2007; Mahoney *et al*, 2004; Wetherby *et al*, 2014; Green *et al*, 2010; Venker *et al*, 2012). Their inclusion may help extend the beneficial effects of treatment even outside the time allotted for therapy.

Limitations of the study must, however, be noted. First, this was a prospective non-controlled study. Indeed, from an ethical and practical point of view, it was impossible to find subjects who had not received any ASD treatment for two years. Another limitation of this study was the limited size of our sample.

In conclusion, this is the first prospective study to suggest positive effects of the 3I method on behavioral and developmental skills and on ASD severity. The results presented in this study are consistent with other methods using play therapy and may represent an advantage of the 3I method, as it is less expensive. However, further studies are needed to support these initial results.

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Table 1. Calendar of outcome assessments

	T0 (+1 month)	T1 (+12 months)	T2 (+24 months)
ADI-R	x	x	x
CARS	x	x	x
VABS	x	x	x
PEP-R	x	x	x
IMITATION (Nadel)	x	x	x

Table 2 Sample description at baseline

Characteristics of subjects at inclusion	
Number	20
Sex	Boys: 18; Girls: 2
Chronologic age (months ± SD)	63.8 ± 37.8
Developmental age (month ± SD, from global PEP-R score)	19.5 ± 6.6
Developmental quotient (mean ± SD from global PEP-R developmental age)	35.3 ± 13.1
Type of communication (%)	Nonverbal: 13 (65%) Gestures: 1 (5%) Babbling: 2 (10%) Verbal: 4 (20%)
Total duration of treatment (hours ± SD)	2832 ± 550

Commenté [Ed3]: Many English-language journals request the use of a period for the decimal place instead of the decimal comma (e.g., 1.00 vs. 1,00). Please consult your journal to determine their preference and make the appropriate changes throughout the manuscript and in any tables or figures.

Table 3

Evaluation	T0	T1	T2	P-value Friedman
VABS Communication (mean ± SD)	**15.8 ± 9.0**	**19.9 ± 10.0*** **	**21.7 ± 11.2*** **	**$1.2.10^{-6}$**
VABS Socialization (mean ± SD)	**12.8 ± 6.5**	**19.2 ± 7.6*** **	**24.3 ± 13.4*** **	**$2.7.10^{-6}$**
Imitation Score Nadel (mean ± SD)	**9.6 ± 5.7**	**13.4 ± 7.1** **	**14.3 ± 6.3** **	**$6.5.10^{-5}$**
PEP-R Imitation (mean ± SD)	**11.2 ± 8.1**	**16.0 ± 11.8***	**18 ± 15.0** **	**$4.5.10^{-5}$**
PEP-R Verbal cognition (mean ± SD)	**17.6 ± 9.4**	**22 ± 13.0**	**20.9 ± 16.0**	**2.07E-01**
Global PEP-R (mean ± SD)	25.7 ± 10.5	30.9 ± 13.5**	33.5 ± 17.0***	5.83E-06
PEP-R Perception (mean ± SD)	28.5 ± 12.6	38 ± 17.7**	40.5 ± 17.1**	4.48E-04
PEP-R Fine motor skills (mean ± SD)	30.6 ± 14.7	35.2 ± 15.0*	39.7 ± 17.2*	0.0147
PEP-R Global motor skills (mean ± SD)	32.3± 12.9	41.0 ± 14.4**	34.0 ± 20.3	8.59E-03
PEP-R Oculo-manual development (mean ± SD)	28.8 ± 14.5	35.5 ± 16.5*	38.8 ± 18.2**	1.12E-03
PEP-R Cognitive performance (mean ± SD)	21.9 ± 14.8	25.5 ± 15.2	26.9 ± 19.0	0.0293
VABS Autonomy (mean ± SD)	23.1 ± 9.7	27.2 ± 10.3***	32.1 ± 12.4***	9.87E-07
VABS Motricity (mean ± SD)	31.6 ± 11.5	37.5 ± 12.4**	38.5 ± 14.1**	2.31E-04

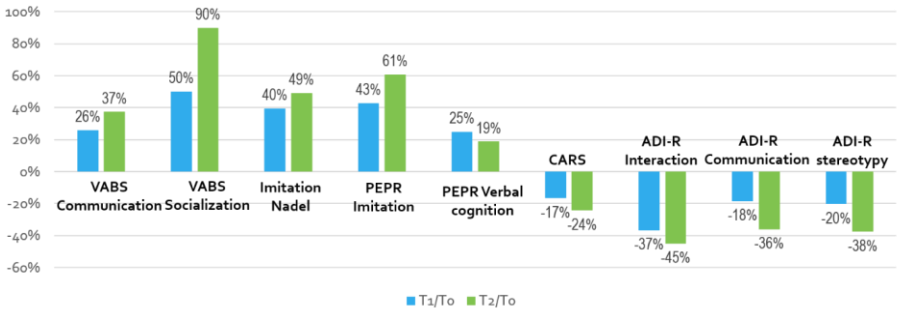
Table 3 Variation in developmental and behavioral skills throughout the study.
All scores are developmental age in months except for the imitation score based on the Nadel scale. The * indicates the level of the p-values of the post hoc tests between T0 and T1 and T0 and T2 after the Friedman test. Bonferroni adjustments were made due to the multiple analyses *** p<0.001; ** p<0.01; * p<0.05

Table 4 Assessment of autism severity during the study

Evaluation	T0	T1	T2	P-value
CARS	44.5 ± 5.0	37.1 ± 5.6**	33.7 ± 5.1***	1.76e-07
ADI-R Interaction	23.1 ± 3.2	14.6 ± 3.8***	12.7 ± 5.0***	1.21e-07
ADI-R Communication	13.0 ± 3.7	10.6 ± 3.1*	8.3 ± 2.8**	4.77e-05
ADI-R Stereotypy	6.4 ± 2.6	5.1 ± 2.5	4.0 ± 2.1*	0.00235

The * indicates the level of the p-values of the post hoc tests between T0 and T1 and T0 and T2 after the Friedman test. Bonferroni adjustments were made due to the multiple analyses *** p<0.001; ** p<0.01; * p<0.05

Figure 1



Graph of the progression in behavioral and developmental skills and autism severity among subjects. The changes in median scores of the VABS developmental age. PEP-R developmental age. Nadel imitation scale and the CARS and ADI-R evaluations are reported according to the T0 values and expressed as a percentage.

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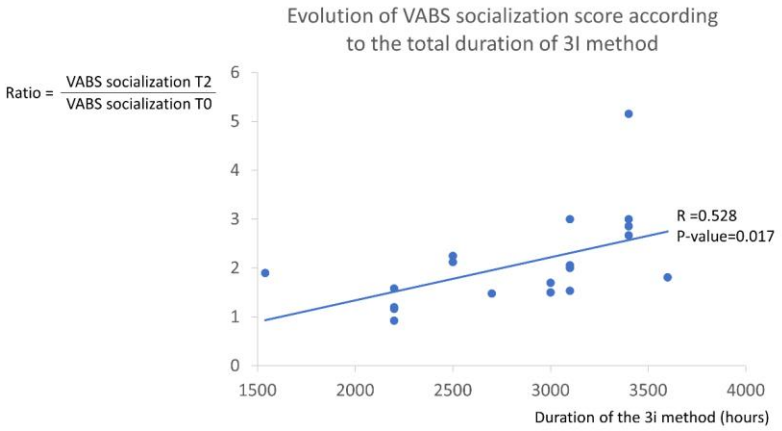
Figure 2



Plot of the duration of the 3I method (in hours) and the ratio of the VABS socialization score at T2 to the VABS socialization score at T0 (baseline). A positive significant positive correlation was found (P-value =0.017) between these two variables.